IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

- - -

| | | |
|---|---|---|
| SHIRE ORPHAN THERAPIES LLC and SANOFI-AVENTIS DEUTSCHLAND GMBH, | ) | Civil Action |
| Plaintiffs, | ) | |
| v. | ) | |
| FRESENIUS KABI USA, LLC, | ) | |
| Defendant. | ) | No. 15-1102-GMS |

- - -

Wilmington, Delaware
Wednesday, January 31, 2018
9:00 a.m.
Trial Day 3

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Senior Judge, U.S.D.C., District of Delaware

APPEARANCES:

JACK B. BLUMENFELD, ESQ., and
DAREN J. FAHNESTOCK, ESQ.
Morris, Nichols, Arsht & Tunnell LLP
-and-
EDGAR H. HAUG, ESQ.,
SANDRA KUZMICH, Ph.D., ESQ.,
LAURA A. CHUBB, ESQ., and
ELIZABETH MURPHY, ESQ.
Haug Partners LLP
(New York, NY)

Counsel for Plaintiffs

**APPEARANCES CONTINUED:**

**KAREN E. KELLER, ESQ.**
**Shaw Keller LLP**
**-and-**
**DARYL L. WIESEN, ESQ.**
**WILLIAM G. JAMES, ESQ.,**
**JOHN COY STULL, ESQ., and**
**SAMUEL SHERRY, ESQ.**
**Goodwin Procter LLP**
**(Washington, DC)**

**Counsel for Defendant**

**- - -**

09:02:23 **THE COURT: Good morning.**

09:02:24 **(Counsel respond "Good morning.")**

09:02:25 **THE COURT: Please, take your seats. I guess it's video time?**

09:02:29

09:02:32 **MS. KUZMICH: Your Honor, plaintiffs are ready to proceed with a live witness, the expert.**

09:02:34

09:02:37 **THE COURT: All right.**

09:02:38 **MS. KUZMICH: Plaintiffs would like to call Dr. Loren David Walensky to the stand.**

09:02:40

09:02:48 **Your Honor, permission to approach the Bench with the witness?**

09:02:51

09:02:53 **THE COURT: Certainly.**

09:03:01 **... LOREN DAVID WALENSKY, having been duly sworn as a witness, was examined and testified as follows ...**

09:03:17

09:03:26 **THE COURT: Good morning, Doctor.**

09:03:27 **THE WITNESS: Good morning.**

09:03:30 **THE COURT: Doctor, I will remind you, please be careful about that step.**

09:03:42

**DIRECT EXAMINATION**

09:04:07 **BY MS. KUZMICH:**

09:04:07 Q. **Would you please state your full name for the record?**

09:04:09 A. **Loren David Walensky.**

09:04:10 Q. **Good morning, Dr. Walensky. What is your current employment?**

09:04:14

09:04:15 A. **I am a professor at Harvard Medical School. I am a**

09:04:18 **research scientist at the Dana Farber Cancer Institute. And**
09:04:22 **I am a physician in pediatric cancer at Boston Children's**
09:04:27 **Hospital.**
09:04:27 Q. **Would you please turn to PTX-264 in the binder that I**
09:04:32 **have handed you. Are you familiar with this document?**
09:04:49 A. **Yes, I am.**
09:04:50 Q. **What is this document?**
09:04:51 A. **It is my CV.**
09:04:52 Q. **Is this information in your CV accurate and up to**
09:04:56 **date?**
09:04:56 A. **Yes, as of September of 2017.**
09:04:59 Q. **Would you briefly describe your educational**
09:05:03 **background?**
09:05:03 A. **Sure. I went to college at Princeton University,**
09:05:07 **where I got a Bachelor of Arts in chemistry and also was a**
09:05:11 **Science Policy Certificate student in the Woodrow Wilson**
09:05:15 **School of Public International Affairs.**
09:05:17 **There I performed synthetic chemistry research**
09:05:19 **in the laboratory of Ted Taylor, where we designed small**
09:05:23 **molecules to target the folic acid pathway in cancer.**
09:05:27 **From there I graduated in 1990 as valedictorian,**
09:05:30 **and went on to Johns Hopkins University School of Medicine**
09:05:34 **where I received both my M.D. and Ph.D. degrees in 1997.**
09:05:40 **There I got my Ph.D. in pharmacology and**
09:05:44 **molecular sciences, in the laboratory of Solomon Snyder, who**

09:05:48 **is a renowned neuroscientist and pharmacologist who**
09:05:53 **specializes in receptor-ligand interactions. That is stated**
09:05:57 **there.**
09:05:57 Q. **Would you briefly describe your professional positions**
09:06:00 **since obtaining your Ph.D. in 1997?**
09:06:05 A. **So from 1997 to 1998, I was a postdoctoral fellow in**
09:06:12 **Solomon Snyder's laboratory, which was postdoctoral research**
09:06:18 **experience in the neurosciences and signaling. From there I**
09:06:21 **went from Baltimore to Boston, where I completed my**
09:06:23 **internship in pediatrics at Boston's Children Hospital and**
09:06:28 **the following year completed my junior residency in**
09:06:31 **pediatrics at Boston Children's Hospital.**
09:06:32 **From there I became a pediatric**
09:06:35 **hematology/oncology fellow. That started in the year 2000.**
09:06:38 **That was a combined program where you trained as a pediatric**
09:06:41 **cancer doctor and also conducted research.**
09:06:44 **And I conducted my postdoctoral research in the**
09:06:47 **laboratory with Dr. Stan Korsmeyer and was co-mentored by**
09:06:51 **Greg Verdine, a chemist at Harvard who specialized in the**
09:06:56 **development of a new technology to stabilize peptides and**
09:07:00 **improve their behaviors so they could be developed as**
09:07:03 **discovery agents but also as new forms of peptide**
09:07:07 **therapeutics.**
09:07:09 **From that position I went to a faculty**
09:07:12 **fellowship at the Harvard Medical School at the Dana Farber**

09:07:17 Center in 2003, then I was promoted as an assistant
09:07:21 professor in 2006, at which point I started my own
09:07:24 independent research laboratory in peptide development.
09:07:27 I was promoted to associate professor in 2011
09:07:30 and was promoted to full professor in 2016. And I became
09:07:34 the medical director of the Harvard and the Massachusetts
09:07:39 Institute of Technology M.D. Ph.D. training program in 2013.
09:07:43 Q. What positions do you currently hold at the
09:07:46 institutions to which you are affiliated?
09:07:47 A. My official titles are professor of pediatrics at
09:07:50 Harvard Medical School. I am a principal investigator in
09:07:53 Cancer Chemical Biology at the Dana Farber Cancer Institute.
09:07:57 I am an attending physician in pediatric oncology at Boston
09:08:03 Children's Hospital. And I am the director of the M.D.
09:08:06 Ph.D. training program at Harvard Medical School and MIT.
09:08:11 Q. Dr. Walensky, during your fellowship in molecular
09:08:14 oncology at Dana Farber, what were your areas of research?
09:08:18 A. So I focused with this co-mentored post-doc between
09:08:23 Stan Korsmeyer and Greg Verdine, which was a fusion between
09:08:26 chemistry and cancer biology, and my project was to develop
09:08:32 a new class of peptides where we would generate them in a
09:08:35 way by using non-natural amino acid substitutions to
09:08:38 generate more potent peptides both in their ability to bind
09:08:41 their targets, but also to withstand protease degradation so
09:08:46 that they can be used both as research tools to discover new

09:08:51 **biology but also to apply them as potential therapeutics.**

09:08:53 Q. **In what areas is your research focused as a principal**

09:08:58 **investigator today?**

09:08:58 A. **So I continued on this theme in my laboratory, which I**

09:09:02 **have had for the past 12 years. What we do is we design**

09:09:05 **peptides, we synthesize them. We characterize and purify**

09:09:10 **them. And then we apply the peptides in biochemical assays.**

09:09:14 **We apply our peptides in cell biology assays.**

09:09:16 **And then we apply our peptides in animal studies looking at**

09:09:20 **their pharmacology, their biological activity, and also then**

09:09:24 **try to translate them into prototype peptide therapeutics.**

09:09:29 Q. **Are there particular types of peptides in which your**

09:09:32 **research is focused?**

09:09:34 A. **Yes. So my research has touched certain areas of**

09:09:37 **biology. I especially emphasized cell death research, so**

09:09:41 **the BCL-2 family proteins that regulate how our cells live**

09:09:45 **and die, which is particularly relevant to cancer, because**

09:09:49 **cancer resistance, recurrence and relapse results from the**

09:09:54 **inability of cells to die.**

09:09:56 **So I focus on those biochemical proteins or**

09:09:59 **actions to try to help cancer cells remember how to die. We**

09:10:03 **also develop peptides for targeting infectious diseases and**

09:10:07 **also endocrinologic diseases like diabetes.**

09:10:10 Q. **What research tools do you use as a principal**

09:10:13 **investigator?**

09:10:13 A. **So I would say my laboratory is multidisciplinary. So**
09:10:17 **we start with chemistry and peptide chemistry in particular.**
09:10:20 **We design new classes of peptides, including new non-natural**
09:10:24 **amino acids that would go into those peptides. We develop**
09:10:28 **chemistries to stabilize the peptides. And then we use**
09:10:31 **biochemical methods, cell biology methods, mouse modeling**
09:10:36 **studies and also structural biology to characterize our**
09:10:39 **peptides and develop them on this pathway toward clinical**
09:10:43 **development.**
09:10:43 Q. **Other than the research you just described, do you**
09:10:47 **have other responsibilities as a principal investigator?**
09:10:49 A. **Yes. So my laboratory has always been in the 16 to 24**
09:10:55 **person range size. And I train undergraduate students in**
09:10:59 **science, I train Ph.D. students from the chemical-biology**
09:11:04 **program, from the biological and biomedical sciences program**
09:11:07 **that spans Harvard and MIT. And I also train postdoctoral**
09:11:11 **fellows, who then go on to start their own laboratories in**
09:11:14 **basic research.**
09:11:15 Q. **Are you involved in any professional activities**
09:11:19 **outside of the university?**
09:11:20 A. **Yes. I serve on the scientific advisory board of**
09:11:24 **several entities, including pediatric cancer foundations,**
09:11:28 **also, I am a consultant and scientific advisor for Aileron**
09:11:32 **Therapeutics, which is a peptide company that I helped**
09:11:35 **co-found as a scientist.**

09:11:36 Q. **Could you provide a little more detail as to what are**
09:11:40 **the activities of Aileron Therapeutics?**
09:11:46 A. **Aileron Therapeutics has licensed a bunch of my**
09:11:47 **patents. What they are trying to do is to commercialize our**
09:11:51 **peptide stapling technology to develop peptide drugs for**
09:11:55 **various diseases. Right now we are focused on cancer. One**
09:12:00 **of the compounds that they licensed and developed from my**
09:12:02 **group is currently in Phase II clinical testing.**
09:12:05 Q. **And you referred to I think stapling peptides. Could**
09:12:09 **you explain a little briefly about what that is?**
09:12:11 A. **Yes. So in order for peptides to work, they need to**
09:12:14 **have a defined structure. And one of the problems with**
09:12:18 **peptides is that they could unfold and change shape and they**
09:12:23 **can lose biological activity.**
09:12:24 **They can also get broken down in the body very**
09:12:26 **quickly.**
09:12:26 **So we developed a way to insert non-natural**
09:12:29 **amino acids into the peptides and then we crosslinked them**
09:12:32 **with a stapling chemistry and essentially put a strut into**
09:12:35 **the peptides so that we don't allow it to unfold, lose its**
09:12:40 **shape, and also to maintain stability so that they have much**
09:12:43 **better properties when you inject them into animals or**
09:12:46 **people.**
09:12:46 **THE COURT: Doctor, I don't mean to be rude.**
09:12:50 **Is this level of detail necessary to qualify**

09:12:53 this witness?

09:12:54 MS. KUZMICH: I will move on, Your Honor.

09:12:56 BY MS. KUZMICH:

09:12:56 Q. Dr. Walensky, have you authored any publications?

09:12:59 A. Yes, over 70.

09:13:00 Q. Have you been elected to any organizations in

09:13:02 recognition for your research?

09:13:03 A. Yes. The Society For Pediatric Research, the American

09:13:07 Pediatric Association, the American Society for Clinical

09:13:10 Investigation, and I just completed my term as the chairman

09:13:13 of the Cancer Molecular Pathobiology study section for the

09:13:18 National Institutes of Health.

09:13:19 THE COURT: What area are you offering him as an

09:13:21 expert in?

09:13:23 MS. KUZMICH: In the field of peptide drug

09:13:26 development, biochemistry, and pharmacology, as an expert.

09:13:29 THE COURT: Any objection?

09:13:30 MR. JAMES: No objection.

09:13:30 THE COURT: It seems the doctor is eminently

09:13:33 qualified, and you are accepted as an expert.

09:13:35 THE WITNESS: Thank you.

09:13:37 BY MS. KUZMICH:

09:13:38 Q. Dr. Walensky, have you provided any demonstratives to

09:13:41 use today?

09:13:42 A. Yes, I have.

08:47:24 Q. **And would you please confirm that those demonstratives**
09:13:26 **appear in the front sleeve of your binder?**
09:13:28 A. **They do.**
09:13:28 Q. **What opinions have you been asked to provide in this**
09:13:33 **case today?**
09:13:33 A. **So I was asked to determine my opinion on whether**
09:13:39 **claim 14 of the '333 patent is not invalid for**
09:13:42 **obviousness-type double patenting over Claim 1 of the '7,803**
09:13:46 **patent in view of the prior art as of January 1989, and the**
09:13:49 **opinion that I've come to is that Claim 14 of the '333**
09:13:53 **patent is not invalid for obviousness-type double patenting**
09:13:57 **over Claim 1 of the '7,803 patent in view of the prior art**
09:14:01 **as of January of 1989. And I base this opinion as**
09:14:05 **summarized here on the definition of a person of ordinary**
09:14:08 **skill in the art in the context of the '333 patent, the**
09:14:13 **meaning of Claim 14 of the '333 patent, the meaning of claim**
09:14:16 **terms in the '7,803 patent, and how a person of ordinary**
09:14:21 **skill in the art would have viewed Claim 1 of the '7,803**
09:14:24 **patent in the context of the prior art.**
09:14:28 Q. **Dr. Walensky, you stated that you formed an opinion as**
09:14:30 **to the definition of a person of ordinary skill in the art.**
09:14:34 **What is your understanding of the term person of ordinary**
09:14:37 **skill in the art?**
09:14:38 A. **It's a hypothetical person who has knowledge of the**
09:14:41 **relevant prior art.**

09:14:42 Q. **And did you arrive at a definition of a person of**
09:14:44 **ordinary skill in the art in the context of the '333**
09:14:48 **patent?**
09:14:48 A. **Yes. I summarized that on PDX-3.2. A person of**
09:14:52 **ordinary skill in the art in the context of the '333 patent**
09:14:56 **is a person who has at least a Ph.D. in organic chemistry,**
09:15:00 **medicinal chemistry, pharmacology, or a similar field, and**
09:15:04 **has a working knowledge of the chemistry and biochemistry of**
09:15:07 **bradykinin or other peptides for the purposes of drug**
09:15:10 **development.**
09:15:11 Q. **Dr. Walensky, are you comfortable today if we use the**
09:15:14 **term POSA to refer to your person of ordinary skill in the**
09:15:17 **art as you have defined it?**
09:15:19 **THE COURT: That's a term I use, Doctor, so you**
09:15:20 **can use that.**
09:15:21 **THE WITNESS: Okay. Yes.**
**BY MS. KUZMICH:**
09:15:24 Q. **Did you consider any information in forming your**
09:15:27 **opinion as to the definition of a POSA in the context of the**
09:15:30 **'333 patent?**
09:15:30 A. **Yes, I did. So if you turn to PDX-3.3, these are the**
09:15:34 **factors: The educational level of the inventors and the**
09:15:37 **workers in the field, the type of problems that were**
09:15:39 **encountered in the art at the time, the prior art solutions**
09:15:42 **to those problems, the rapidity with which innovations were**

09:15:47 **made, and the sophistication of the technology.**

09:15:50 Q. **And generally, Dr. Walensky, how did these factors**

09:15:53 **inform your opinion as to the definition of a POSA?**

09:15:55 A. **So I was informed by counsel that the education level**

09:15:59 **of the inventors and workers at the time had a Ph.D. in**

09:16:03 **synthetic organic chemistry or a Ph.D in pharmacology or**

09:16:08 **were medical doctors, and what they were confronting was**

09:16:11 **that they had a field where hundreds and hundreds of analogs**

09:16:13 **were being made to try to come up with bradykinin**

09:16:16 **antagonists, and one of the major challenges was that the**

09:16:19 **assays that were used were very variable between**

09:16:23 **laboratories and the actual results produced by those assays**

09:16:27 **were also variable between laboratories.**

09:16:29 **Another major problem here was that they**

09:16:32 **did not have the receptor or the target clone, so they**

09:16:36 **didn't know its structure, and so they were basically**

09:16:39 **designing an agonists in a black box.**

09:16:42 **There were some solutions to this, like you**

09:16:44 **could substitute various amino acids in and try different**

09:16:47 **combinations to try to come up with solutions. One of those**

09:16:50 **solutions was substituting a D-phenylalanine for proline and**

09:16:55 **having an antagonist as a result. That was one. That was**

09:16:58 **the start of the field in these antagonists. But**

09:17:01 **innovations were slow. It took over 25 years to come up**

09:17:04 **with that peptide and it also took hundreds and hundreds of**

09:17:08 **analogs to come upon it.**

09:17:10 Q. **So is it the case that is the information that**

09:17:14 **informed your opinion as to the definition of a POSA on**

09:17:17 **DXT-3.2?**

09:17:18 A. **Yes. That's the context.**

09:17:20 Q. **Dr. Walensky, would your opinion as to whether Claim**

09:17:22 **14 of the '333 patent is invalid for obviousness-type double**

09:17:25 **patenting over Claim 1 of the '7,803 patent change if the**

09:17:30 **Court accepts Dr. Bachovchin's definition of a POSA?**

09:17:34 A. **No.**

09:17:36 Q. **Dr. Walensky, going back to your opinions listed on**

09:17:39 **PDX 3.1, you state that you formed an opinion as to the**

09:17:44 **meaning of Claim 14 of the '333 patent; is that correct?**

09:17:46 A. **Yes.**

09:17:47 Q. **What is your opinion as to the meaning of Claim 14 of**

09:17:49 **the '333 patent?**

09:17:52 A. **So if you go to PDX-3.4, I explained my interpretation**

09:17:56 **of the meaning of Claim 14 of the '333 patent, which is**

09:17:58 **entitled, peptides having bradykinin antagonist action. The**

09:18:03 **claim is written there. A POSA would have interpreted Claim**

09:18:06 **14 of the '333 patent as a peptide of a formula**

09:18:11 **D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH or a**

09:18:20 **physiologically tolerable salt peptide of said peptide with**

09:18:24 **bradykinin antagonist activity.**

09:18:24 Q. **Did you consider any information in coming to your**

09:18:26 opinion as to the meaning of Claim 14?
09:18:27 A. Yes, I did. If we turn to PDX-3.5. I summarized the
09:18:32 basis for my opinion from the language of Claim 14, the
09:18:35 title of the patent, the abstract, statements throughout the
09:18:38 patent, and the biological data.
09:18:40 Q. So let's begin with the language of Claim 14, Dr.
09:18:44 Walensky. Please turn to JTX-1.24 at column 44, line 44
09:18:50 through 46. That is Claim 14 of the '333 patent.
09:18:56 Would you please explain how that language of
09:18:58 the claim informed your opinion.
09:18:59 A. So in column 44, we are at line 44. It says, a
09:19:06 peptide of the formula of
09:19:09 D-Arg-Arg-Pro-Hyp-Gly-Thia-Ser-D-Tic-Oic-Arg-OH or a
09:19:17 physiologically tolerable salt of said peptide.
09:19:22 Q. You said you also considered information on JTX-1.2,
09:19:28 which is the face of the patent. If you could turn to
09:19:30 JTX-1.2 and explain what information you considered on the
09:19:34 face of the patent to form your opinion?
09:19:34 A. -- so I read the title and it says, peptides having
09:19:37 bradykinin antagonist action.
09:19:38 Q. And did you consider any other information on the face
09:19:41 of the patent?
09:19:41 A. I read the abstract and the abstract describes the
09:19:44 peptide of the formula I again, and then it says, it says
09:19:49 that this is the formula I that's described here. I will

09:19:53 quote, have bradykinin antagonist action for therapeutic
09:19:57 utility. Their therapeutic utility includes all
09:20:02 pathological states which are mediated, caused or supported
09:20:05 by bradykinin and bradykinin related peptides.
09:20:07 Q. What does it mean to have bradykinin antagonist
09:20:10 action?
09:20:10 A. So basically it's a peptide that you would make that
09:20:12 would prevent the natural peptide from binding to its
09:20:15 receptor. So it's essentially a disruptor of the natural
09:20:18 interaction between the hormone and the receptor.
09:20:21 Q. Looking at bullet point 4 on PDX-3.5, you say that you
09:20:27 considered statements in the patent specification. What
09:20:29 statements did you consider in the patent specification of
09:20:31 the '333 patent?
09:20:32 A. So if you go to Column 1 and just look at line 44, it
09:20:37 says, the present invention relates to novel peptides having
09:20:41 bradykinin antagonist action and to a process for their
09:20:45 preparation.
09:20:46 And then if you continue down to line 53,
09:20:49 it says, the present invention is based on the object of
09:20:52 finding novel active peptides having bradykinin antagonist
09:20:56 action.
09:20:57 Q. And, Dr. Walensky, finally, if you could focus on your
09:21:01 last bullet point on PDX 3.5 referring to the biological
09:21:06 data of the '333 patent, what biological data do you

09:21:10 consider, please?
09:21:11 A. So spanning Column 16 and 17, there's a table that
09:21:14 lists peptides, and then on the --
09:21:17 THE COURT: If you could get rid of those arrows
09:21:19 if you hit the screen or something? Yes. Thank you.
09:21:23 THE WITNESS: So in Table 1 there's a list of
09:21:25 peptides, and on the right-hand column there's a list of
09:21:28 numbers that are, you know, headed by IC 50.
09:21:31 So it's looking at the inhibitor concentration
09:21:34 of these peptides that's required to block the peptide's
09:21:38 ability to bind to its receptor by 50 percent, and all the
09:21:41 peptides listed here have bradykinin antagonist action.
09:21:44 Q. Doctor, is the peptide of Claim 14 of the '333 patent
09:21:49 in Table 1?
09:21:49 A. It is. It's the one two-thirds down that has a
09:21:54 reading of 5.4 times ten to the minus nine. That's the
09:21:58 peptide and it has bradykinin antagonist action.
09:22:00 Q. Dr. Walensky, in your view of the '333 patent, did any
09:22:04 of the peptides of the invention have biological activity
09:22:08 other than bradykinin antagonist action?
09:22:10 A. No.
09:22:11 Q. Based on the information in the '333 patent, how would
09:22:14 a person of ordinary in the art construe Claim 14?
09:22:17 A. They would look at the claim. They would see the
09:22:20 composition that was indicated, and it indicates by looking

09:22:24 at that in the context of this, that the peptide composition
09:22:28 is patented because of bradykinin antagonist action.
09:22:30 Q. Dr. Walensky, would your opinion as to whether
09:22:32 Claim 14 of the '333 patent is invalid for obviousness-type
09:22:37 double patenting change if the Court accepts Dr.
09:22:42 Bachovchin's construction of Claim 14?
09:22:43 A. No.
09:22:44 Q. Dr. Walensky, I'd like to move on to the topic of
09:22:47 obviousness-type double patenting. And you testified
09:22:50 earlier that you concluded that claim 14 of the '333 patent
09:22:56 is not invalid for obviousness-type double patenting over
09:22:59 Claim 1 of the '7,803 patent; is that correct?
09:23:03 A. Yes.
09:23:04 Q. Would you please provide us the basis for this
09:23:06 opinion.
09:23:07 A. Okay. So on PDX-3.6, I summarized the basis for my
09:23:12 opinion.
09:23:14 Number one, a POSA would have interpreted
09:23:15 the claim term Z-P-A-B-C-E-F-K-(D)Q-G-M-F'-I, a peptide of
09:23:25 the Formula I in Claim 1 of the '7,803 patent to mean a
09:23:28 peptide with a Z group, which is an N terminal modification
09:23:32 that is an integral and permanent component of the final and
09:23:36 claimed peptide product. This interpretation is solely
09:23:39 based on the language of Claim 1.
09:23:42 The claim term P language is also informative as

09:23:46 to the meaning of the peptide of Formula I.

09:23:48 The second point is that in addition to the
09:23:50 language of Claim 1, Claims 2 and 3 and also the
09:23:53 specification of the patent demonstrate that a peptide of
09:23:57 the Formula I in Claim 1 of the '7,803 patent means a
09:24:01 peptide with a Z group, which is an N terminal modification
09:24:04 that is an integral and permanent component of the final and
09:24:09 claimed peptide product.

09:24:10 Third, in view of the prior art as of January of
09:24:13 1989, a POSA would not have been motivated to remove the
09:24:17 N-terminal modifications of the peptides of Claim 1 of the
09:24:21 '7,803 patent when creating a bradykinin antagonist. It was
09:24:24 expressly taught to include in bradykinin antagonists
09:24:30 permanent N-terminal modification such as the Z groups that
09:24:33 are listed in Claim 1 of the '7,803 patent.

09:24:36 And, finally, point 4. As of January 1989, a
09:24:41 POSA that was confronted with D-Tic at position seven or Oic
09:24:46 at position eight, in the context of a peptide that
09:24:50 otherwise appears to be a bradykinin analog, would have had
09:24:54 no reasonable expectation of success that such a peptide
09:24:57 would have bradykinin antagonist action.

09:25:00 Q. Dr. Walensky, to make this conversation a bit easier,
09:25:04 if we could agree that the claim term
09:25:08 Z-P-A-B-C-E-F-K-(D)Q-G-M-F'-I, that we could refer to that
09:25:16 as a peptide of the formula I.

09:25:19 A. **Yes.**

09:25:19 Q. **Thank you.**

09:25:21 **You state on PDX-3.6 that your first point is**
09:25:25 **just based on the language of Claim 1, a person of ordinary**
09:25:28 **skill would have interpreted the peptide of formula I to**
09:25:32 **mean a peptide with a permanent Z group, and I will**
09:25:36 **abbreviate that not to read your whole definition or**
09:25:39 **position in.**

09:25:39 **If you would please then provide us with your,**
09:25:43 **a summary of why you considered the claim language of Claim**
09:25:48 **1.**

09:25:49 A. **Sure. So if you turn to PDX-3.7, I list the basis for**
09:25:53 **my opinion, which is, the language of Claim 1 itself. The**
09:25:58 **common chemical features of all of the Z groups that**
09:26:02 **indicate permanence, and the option for the P group.**

09:26:05 Q. **If you would please turn to DTX-59_0011, which is**
09:26:12 **Claim 1 of the '7,803 patent.**

09:26:19 **How did the language of Claim 1 inform your**
09:26:22 **opinion as to the meaning of a peptide of the formula I?**

09:26:25 A. **So one just reads the language. It says there on**
09:26:35 **column 20, line 21, a peptide of a formula I, and it lists**
09:26:40 **the composition, Z-P-A-B-C-E-F-K-(D)-Q-G-M-F'-I in which,**
09:26:49 **and I will continue reading Z, is, and it lists several**
09:26:53 **chemical choices. Fmoc, dibenzylacetyl, cyclohexylcarbonyl,**
09:27:00 **N-N-dibenzyl-glycyl, 2(4-isobutylphenyl) propionyl, (2-R**

**tert butylsulfonylmethyl)-3-(1-naphthyl) propionyl, indole-3-yl-acetyl, 6-(4-benzoyl-benzoylamino) hexanoyl, 1, 8-naphthalimidoacetyl, 7-theophyllineacetyl or N-benzoyl.**

09:27:23 **And then if you continue, P is a direct linkage, Aoc, epsilon-aminohexanoyl, D-Aoc, Aeg(Fmoc), 4-aminocyclohexylcarbonyl or Oic.**

09:27:39 **So what I mean by reading that language, D gives you 11 choices. P gives you seven choices. One of the choices for P is not to use P. The option not to use Z is not listed among the choices for Z.**

09:27:56 **So just by reading that plain language, a POSA recognizes that this composition contains one of those 11 Z groups in the claimed peptide. But for the P, they are very clear that you could have one of those six chemical additions or not include them at all. And that option of not including it at all is explicitly not listed in Z. So the interpretation of the POSA is, my claimed peptide has to have a Z as a permanent component of that claimed composition.**

09:28:41 Q. **You also state on PDX-3.7 that you looked at a common chemical feature of all the Z groups that indicate permanence. Could you please explain what you mean by that statement?**

09:28:55 A. **Yes. To simplify I prepared PDX-3.8.**

09:29:01 Q. **What this slide shows, this is bradykinin peptides**

09:29:05 with modifications at the N-terminus. That is the title of
09:29:08 the patent. What I am showing you here are all of the
09:29:11 pictures, the structures of what those 11 Z groups could be
09:29:16 that are listed under the Z group as choices.
09:29:19 Now, if you go to the next clip, what you will
09:29:22 see is that the common feature for every single one of these
09:29:26 choices is an acyl group highlighted in purple. That is
09:29:31 kind of your entry to the club, so to speak. That is what
09:29:34 gets you into the Z club, that you have the acyl group.
09:29:39 I wanted to also point out that Fmoc, which is
09:29:41 the first structure listed, has an extra feature, which is
09:29:44 that O. And that is an oxygen.
09:29:46 Now, the combination of that green O and the
09:29:49 purple acyl group gives you a new chemical name called
09:29:53 urethane.
09:29:54 So what you are seeing in that list are all acyl
09:29:58 groups and Fmoc has an extra name, it is an aromatic
09:30:01 urethane. And again, the card-carrying entry point to get
09:30:05 into this group is the purple highlighted commonality, and
09:30:08 again there is no option for omitting the permanent Z group
09:30:12 in the explicit language of the claim.
09:30:15 Q. Dr. Walensky, you also stated on PDX-3.7 that the
09:30:19 options for the P group informed your opinion as to the
09:30:23 meaning of the peptide of Formula I. Could you explain your
09:30:26 opinion that you stated there with respect to the P group?

09:30:30 A. **Sure. So I do the same thing in the next slide,**
09:30:33 **PDX-3.9, for P. For P, again, I just summarized the**
09:30:37 **chemical structures for you of the six chemical choices.**
09:30:41 **And there they are. And what you will notice here is that**
09:30:45 **in addition to these one of six choices that you can make to**
09:30:49 **insert at the P position, there is the option of no choice,**
09:30:53 **which is what I read right from the claim language.**
09:30:56 **So the key point to make here in looking at P**
09:30:59 **is, if we go to the next panel there, that they are, in**
09:31:02 **clear contrast to the prior slide, the P series includes all**
09:31:06 **of those six choices and a direct linkage, which means none**
09:31:12 **of the above, meaning no P at all.**
09:31:14 **That specific direction is not given for the Z**
09:31:18 **groups. The option of not having a permanent group in the Z**
09:31:21 **position is not indicated in this explicit language of this**
09:31:25 **claim.**
09:31:26 Q. **Dr. Walensky, in staying with the P group for a**
09:31:30 **moment, did you rely on any other information in determining**
09:31:33 **how a POSA would interpret the meaning of the claim term P**
09:31:37 **in the context of the '7,803 patent?**
09:31:40 A. **Yes. So I summarized these also in PDX-3.10.**
09:31:44 **In terms of claim term P, my support for this**
09:31:48 **opinion is the explicit language of Claim 1, the examples,**
09:31:52 **and the biological data.**
09:31:55 Q. **I think we have gone through the explicit language of**

09:31:59 **Claim 1. If you could take a look, and you identified the**
09:32:03 **examples in the '7,803 patent, what did you consider with**
09:32:07 **respect to the examples of the '7,803 patent?**
09:32:14 A. **So this patent lays out 26 examples in Columns 18 to**
09:32:19 **20. And I want to pick out a few to highlight my point.**
09:32:23 **In Example 5, you will see that the Z, the**
09:32:25 **permanent Z position there is Fmoc. And then in the P**
09:32:29 **position, the choice is to include epsilon-aminohexanoyl.**
09:32:34 **That is an example where both a Z and a P were selected to**
09:32:38 **be a part of the final product.**
09:32:40 **If you then go down the examples, example 14,**
09:32:42 **here is an example again where a permanent Z group Fmoc was**
09:32:48 **selected to be in the final composition of the product. And**
09:32:50 **for the P position, another chemical of those choices for P**
09:32:55 **were selected, this one is called Aeg(Fmoc).**
09:32:59 **So this P position is Aeg(Fmoc.). that P**
09:33:03 **position also happens to have an Fmoc as well as a permanent**
09:33:08 **feature of that P position. This example is a peptide that**
09:33:11 **actually has two permanent Fmoc groups in it.**
09:33:14 **Then if you go down to Example 22, you see that**
09:33:17 **exact same scenario again, where the inventors made a**
09:33:20 **peptide where they picked Fmoc for the permanent Z position**
09:33:23 **and they picked Aeg(Fmoc) for the permanent P position,**
09:33:28 **another peptide that was designed to have two permanent Fmoc**
09:33:31 **groups in the final claimed product.**

09:33:33 Q. **Dr. Walensky, you also state on PDX-3.10 that you looked at the biological data in the '7,803 patent to understand more about claim term P. If you could turn to DTX-059_0008 to 0009, how does that information inform your opinion about the P group?**

09:33:59 A. **Okay. Let's look at the P biological data, which is Column 14, Table 1.**

09:34:05 **The first thing to say is that every single peptide listed in this table has a permanent Z group in it. Some of them have permanent P groups in them as well.**

09:34:15 **If you look at 5, the example that I just read that starts with the permanent Fmoc, and it has the P group selected, epsilon-aminocaproyl, that has an IC50 or the ability to block bradykinin activity at 50 percent by the number 4.1 times 10 to the minus 9th.**

09:34:36 **I want to point out that that is the most potent peptide in the table. So if I was a POSA looking at this table I would say, the best peptide of all of the ones tested had a permanent Z group and a permanent P group.**

09:34:54 **That is another point that I want to highlight.**

09:34:56 **If you go down to another example, like 14, there is an example where they have a permanent Fmoc in the Z position, and they have a permanent P group in the Aeg(Fmoc) chemical. This is a peptide that has two permanent Fmoc groups in it. That, too, has bradykinin**

09:35:13 antagonist activity.

09:35:15 So I just want to highlight that the P position,
09:35:18 although not having a P was certainly an option just for P,
09:35:22 the best compound in that list has a P in it.

09:35:26 Q. Dr. Walensky, on one of your summary slides you also
09:35:32 said that you considered Table 2 in the '7,803 patent. If
09:35:36 we could just turn to Table 2 at DTX-05_0009, could you
09:35:43 explain briefly how Table 2 informed your opinion with
09:35:47 respect to the P group?

09:35:48 A. Sure. I mean, this is a different assay now. But
09:35:51 it's comparing 5 different peptides. What you will notice
09:35:54 if you look at the right-hand column, in this case, the
09:35:57 bigger number means better, longer duration of action.

09:36:01 If you just picked out the top two performers in
09:36:04 this table, it's the one that says 253.3 minutes, and the
09:36:09 best is the one that says 314.4 minutes.

09:36:15 Compound 2 has a permanent Fmoc group and a
09:36:18 permanent P group of the choice Aoc. And the best one in
09:36:22 the table, No. 5, has a permanent Fmoc group in the Z
09:36:26 position and a permanent P group selected from the chemical
09:36:29 choice epsilon-aminocaproyl.

09:36:32 So a POSA looking at this and the prior table
09:36:35 would say, some of the best performers in this patent have
09:36:38 the permanent Z group and a permanent chemical choice for
09:36:41 the P group.

09:36:43 Q. **Dr. Walensky, if you can just summarize, again,**
09:36:49 **briefly, your opinion as to the meaning of the claim term P**
09:36:53 **in this group, given your review of the claim language**
09:36:56 **itself and all the information in the specification?**
09:37:00 A. **Simply put, P gives you six different chemical choices**
09:37:04 **to install into this composition or none of the above. But**
09:37:07 **there is no prioritization of what I say, better or worse.**
09:37:10 **They tried a whole bunch of different things. It turned out**
09:37:12 **that actually having a P group, not omitting it, gave you**
09:37:16 **some of the best peptides in the patent. That is what I**
09:37:20 **wanted to point out.**
09:37:20 Q. **Dr. Walensky, if you could turn back to your PDX-3.6.**
09:37:24 **Let's refocus on the meaning of the claimed peptide of**
09:37:30 **Formula I. You said that you relied on other information in**
09:37:33 **the '7,803 patent beyond the language of Claim 1. What**
09:37:37 **other information did you rely on beyond the language of**
09:37:40 **Claim 1 for the definition of a peptide of Formula I?**
09:37:44 A. **So I summarize that in PDX-3.11.**
09:37:49 **The support that I relied on, in addition to the**
09:37:52 **plain claim language of claim 1 was the language in Claims 2**
09:37:54 **and 3, and within the specification the title, abstract,**
09:37:59 **examples, biological results, and the description of how the**
09:38:05 **peptides were actually, ade by the inventors.**
09:38:05 Q. **So let's start with your first bullet point which says**
09:38:10 **that you relied on Claims 2 and 3.**

09:38:15 **Would you please turn to DTX-059_0011 at Column**
09:38:22 **20, Lines 50 through 57. That should bring us to Claims 2**
09:38:27 **and 3 of the '7,803 patent.**
09:38:31 **Would you explain, Dr. Walensky, how Claims 2**
09:38:34 **and 3 informed your opinion as to the meaning of the Z and**
09:38:37 **the peptide of Formula I?**
09:38:38 A. **Sure. So Claim 2 says, "A method for the treatment of**
09:38:42 **inflammation in a mammal wherein the inflammation is**
09:38:45 **mediated, induced or assisted by bradykinin or peptides**
09:38:50 **related to bradykinin, which comprises administering to said**
09:38:55 **mammal an anti-inflammatorily effective amount" -- this is**
09:38:57 **where it gets important -- "of a peptide of the Formula I as**
09:39:01 **claimed in Claim 1."**
09:39:04 **It is very explicit. It's claiming the**
09:39:08 **composition of the peptide formula as claimed in Claim 1,**
09:39:13 **which is shown above, of what that composition is.**
09:39:15 **Then it reiterates in Claim 3, "a pharmaceutical**
09:39:19 **composition," meaning the drugs, "containing a peptide of**
09:39:22 **the Formula I," and again, please underscore, "as claimed in**
09:39:28 **Claim 1."**
09:39:29 **That's the drug, what's claimed in Claim 1.**
09:39:33 Q. **Dr. Walensky, you also said on PDX-3.11 that you**
09:39:38 **looked at the title of the '7,803 patent to form your**
09:39:43 **opinion. Would you please turn to the title and inform us**
09:39:48 **about how that helped you with your opinion?**

09:39:51 A. **Sure. The title of the patent, simply reading the**
09:39:55 **words, Bradykinin Peptides With Modifications At The**
09:39:58 **N-Terminus. So the title is telling you what this patent is**
09:40:03 **about. It's about bradykinin peptides with modifications at**
09:40:07 **the N-terminus.**
09:40:08 Q. **You also indicated that, on the face of the patent,**
09:40:12 **you relied on the abstract to help form your opinion. Would**
09:40:16 **you please explain the bases for how the abstract informed**
09:40:19 **your opinion?**
09:40:20 A. **If you read the abstract it lists that formula again,**
09:40:22 **which I won't re-read, and then it says they have an**
09:40:26 **excellent bradykinin antagonistic action.**
09:40:29 Q. **You also stated that you looked at the examples of the**
09:40:34 **peptides in the '7,803 patent. I know those examples are at**
09:40:38 **DTX-059_0010-_0011 --**
09:40:46 **THE COURT: Counsel, it would be a lot quicker**
09:40:48 **if you referred to the column and the line. I know my way**
09:40:51 **around a patent.**
09:40:53 **MS. KUZMICH: Yes, Your Honor.**
09:40:53 **BY MS. KUZMICH:**
09:40:54 Q. **If you would turn to those examples and explain**
09:40:57 **briefly how those examples informed your opinion as to the**
09:40:59 **meaning of the Z in the peptide Formula I?**
09:41:02 A. **These are examples of all of the final peptides that**
09:41:05 **were made for this patent and all 26 have a permanent Z**

09:41:09 group, every one.

09:41:10 Q. Again, briefly, you said that the biological data

09:41:12 informed your opinion. And if you can just turn to Columns

09:41:15 14 and 15 at Table 1, and explain how that data informed

09:41:19 your opinion?

09:41:20 A. This is the same story. It's the 26 peptides. And

09:41:23 they test them all, in a biological activity assay, every

09:41:29 single peptide in this list has a permanent Z group. Twelve

09:41:32 out of 26 of these have a permanent Fmoc group, selected as

09:41:35 the Z group, and every one of these that were tested has

09:41:42 bradykinin antagonistic action.

09:41:43 Q. Dr. Walensky, finally, you identify that the synthesis

09:41:46 of the peptides described in the '7,803 patent support your

09:41:50 opinion as to what is the meaning of Z in the peptide of

09:41:54 Formula I.

09:41:56 If you could turn your attention to that point

09:41:59 and please let us know how the synthesis of the peptides in

09:42:03 the '7,803 patent informed your opinion?

09:42:05 A. Right. This is very important because this is

09:42:07 actually telling you how to make the peptide of the

09:42:10 invention.

09:42:11 I want to start out on Column 13 reading very

09:42:14 briefly, Ms. Debonis, this is the paragraph that starts out,

09:42:19 When Fmoc protected group was used for temporary protection

09:42:22 of the amino group.

09:42:24 **I want to highlight on Column 13 the sentence**
09:42:26 **that starts with, "The Fmoc," "The Fmoc protective group was**
09:42:31 **eliminated with a 20 percent strength solution of piperidine**
09:42:35 **in DMF in the reaction vessel."**
09:42:39 **You can stop there.**
09:42:41 **This is the on and off aspect of Fmoc, where you**
09:42:45 **put it on, you take it off. This is the reaction that's**
09:42:48 **used to remove Fmoc from a peptide while it's under**
09:42:53 **construction.**
09:42:54 **We are going to talk about this in a minute in**
09:42:56 **the context of a full-bore explanation of the synthesis.**
09:42:59 **Why don't we get right to that at Column 18.**
09:43:05 **If you go to Column 18, in Example 1, they**
09:43:08 **really expand upon this point to tell the reader how to make**
09:43:12 **this peptide. I am going to just walk you through this very**
09:43:15 **briefly.**
09:43:17 **They list the sequence of the peptide and they**
09:43:19 **say that it was assembled step-wise using the Fmoc method on**
09:43:22 **a p -- benzyloxybenzyl alcohol-resin.**
09:43:26 **This is the concept of building a peptide on a**
09:43:29 **resin, putting pearls on a string. That is what this is**
09:43:32 **referring to, building a peptide using the Fmoc method where**
09:43:36 **you take the Fmoc on and off and on and off as you build the**
09:43:40 **peptide under construction.**
09:43:41 **As you go on it talks about how you add an amino**

09:43:45 acid at the time. Let's go down, in the interests of time,
09:43:47 to that part where it says, "The resin which had previously
09:43:51 been deblocked." It's around two-thirds of the way down
09:43:55 there.
09:43:56 We have been adding all these amino acids to the
09:43:59 resin which had previously been deblocked with 20 percent
09:44:02 piperidine. That means we are ready to go to put on another
09:44:06 amino acid and we are taking the Fmoc group off with 20
09:44:09 percent piperidine. That is the chemical that takes it off.
09:44:12 Here is the most important thing.
09:44:14 The last amino acid derivative coupled on was
09:44:19 Fmoc-D-Arg-Pmc-OH. Now, in contrast to everything that has
09:44:26 been described up until this point, now we are adding the
09:44:29 last amino acid. This is the one that is added to the
09:44:32 N-terminus of the peptide.
09:44:35 And that last amino acid has this Fmoc group on
09:44:38 it.
09:44:38 Here is the most important phrase, "which was
09:44:42 not subsequently deprotected with piperidine."
09:44:48 So although everything above that is talking
09:44:51 about on and off, on and off, Fmoc, as you make the peptide,
09:44:55 now we have a very clear distinction. Now we are putting
09:44:58 the last one on, which has the Fmoc, and we are keeping it
09:45:02 on. How do we know that? Because it explicitly and clearly
09:45:06 states "which was not subsequently deprotected with

09:45:10 **piperidine."**

09:45:12 **Then we are done. After the synthesis was**
09:45:14 **complete, what does "being done" mean? Let's highlight**
09:45:18 **this. It means the peptide was cleaved off the resin with**
09:45:22 **simultaneous removal of the side chain protective groups.**
09:45:27 **Then we are done. We have made our pure product.**

09:45:31 **This is a lot of language. It's a lot of**
09:45:34 **methodology. And I think what would be most helpful would**
09:45:37 **be to take this exact methodology that I have just read and**
09:45:41 **show a picture of what it is, to put it into clearest**
09:45:46 **possible context.**

09:45:48 **So I prepared basically a schematic of exactly**
09:45:51 **this language from the '7,803. So this is the '7,803**
09:45:56 **patent's chemical process of constructing peptides on a**
09:46:00 **resin, so that you have permanent N-terminal Z groups. On**
09:46:04 **the right is the resin, which, I am picturing that as a**
09:46:10 **brown ball. The amino acid backbone is shown in blue.**
09:46:13 **Certain amino acid side chains need to be protected during**
09:46:16 **the synthesis or else they will react in an unwanted way.**
09:46:20 **So I am symbolizing that as a red side chain protecting**
09:46:24 **group.**

09:46:25 **Then we get to the N-terminus protecting group**
09:46:27 **of that amino acid, pictured as a green box. That is your**
09:46:32 **Fmoc. That is what comes on and off, on and off, during the**
09:46:35 **peptide synthesis that is under construction.**

09:46:37 **Now let's make this peptide.**

09:46:39 **We are going to remove the Fmoc group with 20 percent piperidine, pops right off, you add your next subunit. You are going to do it again, deprotect with piperidine, remove the Fmoc group on the resin, add your next subunit.**

09:46:53 **We are going to do it again. Deprotect the Fmoc. Add the next subunit. My last example of this same process, automated process, remove the Fmoc, add the next group, there you go.**

09:47:04 **So you keep doing this until you are done making your peptide on the resin.**

09:47:09 **At that point, a decision is made. Are we going to have an N-terminal protecting group on this peptide? This patent is about N-terminal modifications. The answer is, yes, we are. The decision is made to establish a permanent N-terminus protected peptide. How do you do that?**

09:47:25 **Well, in this case, for some of the examples, the inventors just left on the Fmoc group, which is what I just read from '7,803, the last one, which was not removed.**

09:47:35 **So what do they do? They leave it. They cleave the peptide off the resin. And what they get as the final pure product is an Fmoc protected peptide.**

09:47:45 **I specifically changed the color there from green to purple because now we are in a final product. We**

09:47:52 have chosen not to remove the Fmoc. We are leaving it on.

09:47:55 Once that decision is made, we finish off the

09:47:58 synthesis by cleaving, we remove the resin, we remove the

09:48:01 red groups, and we are done.

09:48:03 That is only one example of the Z group. This

09:48:06 patent gave 11 examples. What if we didn't want Fmoc. What

09:48:09 if we wanted one of the other ten? What do we do?

09:48:12 What they would do is they again remove that

09:48:15 Fmoc group while it's on the resin. Everything is

09:48:18 protected. And then they just stick on another N-terminal

09:48:21 modification and they say we like that acyl group, we pick

09:48:25 any of the ten out of the 11 acyl groups that are left over.

09:48:28 And we are done.

09:48:30 So we cleave. We take the resin off. We take

09:48:32 the protecting groups off. And we end up with our final

09:48:35 product, an acyl peptide.

09:48:37 This is the process for making bradykinin

09:48:40 peptides with modifications at the N-terminus.

09:48:44 To summarize that in the clearest way that I

09:48:47 can, I have one more slide on this, which is PDX-3.13, I

09:48:52 think this is so important in this particular case.

09:48:55 Fmoc plays different functional roles in

09:49:00 different contexts.

09:49:02 One context is when a peptide is under

09:49:06 construction. So you have a nascent peptide. It is on the

09:49:10 **resin. It is being made. The side chains are protected as**
09:49:13 **shown in red. The N-terminal Fmoc group can be removed,**
09:49:18 **absolutely can be removed on and off and on and off. And**
09:49:20 **that's what the '7,803 method says, The Fmoc protective**
09:49:24 **group was eliminated during construction when it was chosen**
09:49:27 **to be eliminated with this 20 percent piperidine.**
09:49:17 **That cannot be conflated, confused,**
09:49:20 **brushed under the rug to the second completely**
09:49:24 **scientifically precise alternative choice, which is that**
09:49:27 **when a peptide is complete, and you see an Fmoc or an acyl**
09:49:32 **group or any of those 11 choices that are the Z group, this**
09:49:35 **peptide is off the resin. The side chains are deprotected.**
09:49:40 **The N-terminus Fmoc group is not removed or an acyl group is**
09:49:44 **put there in its place.**
09:49:45 **At this point we are dealing with a purple**
09:49:48 **permanent protecting group and the language that proves it**
09:49:50 **is the last amino acid derivative coupled on with Fmoc D-Arg**
09:49:56 **which was not subsequently deprotected. It is clear as day,**
09:50:00 **and what's very important, if I could make one point that**
09:50:04 **everybody remembers from my time here is, do not be fooled**
09:50:07 **that there's only one functional role for Fmoc. This patent**
09:50:12 **clearly states that Fmoc can do two completely different**
09:50:16 **things. Yes, on/off, on/off, removable. Everybody knows**
09:50:22 **it. That was the discovery that gave you Fmoc solid-phase**
09:50:26 **synthesis, but that doesn't mean that when a chemist decides**

09:50:30 to keep it there, that it's not doing a different role. It
09:50:33 has a different function in that context, and that context
09:50:37 is summarized under number two, and that context applies for
09:50:40 Fmoc and every single Z group listed in this patent, and the
09:50:45 option of not having that is not there.
09:50:47 Q. Dr. Walensky, if you could just summarize your opinion
09:50:50 as to the claim term a peptide of the formula I in claim 1?
09:51:00 A. Those are -- those are peptides that have a Z group.
09:51:06 Q. Moving on to your next topic, Dr. Walensky, you said
09:51:10 on PDX-3.6 that in view of the prior art as of January 1989,
09:51:16 a POSA would not have been motivated to remove the
09:51:19 N-terminal modification of the peptide in Claim 1 because it
09:51:23 was expressly taught to be included in bradykinin
09:51:26 antagonists. And could you -- is that the case?
09:51:29 A. Yes.
09:51:30 Q. And what information did you consider in forming that
09:51:34 opinion?
09:51:34 A. Okay. So now we're moving on from how you actually
09:51:38 make these and how the inventors told us to make it with a
09:51:41 permanent Z group to a different question, which is, if you
09:51:44 saw that, would there be anything that would tell you to
09:51:46 take it off, and I'm going to show you the reasons why in
09:51:49 the literature there are multiple examples of why you would
09:51:52 absolutely keep that Z group in place, so that's what this
09:51:56 portion of my testimony is about. And I summarize it on

09:51:59 **PDX-3.14. I use patent '963. I use an article by Barabe**
09:52:05 **and Regoli. I use patent '204 and a plain old chemistry**
09:52:10 **textbook.**
09:52:10 Q. **Doctor, let's begin with the first reference, the**
09:52:15 **'963 patent. And how did that document inform your**
09:52:18 **opinion?**
09:52:18 A. **I looked at the general peptide structure and**
09:52:21 **modification. I looked at the examples and biological**
09:52:27 **data.**
09:52:29 Q. **What do you mean on PDX--3.15 by the general peptide**
09:52:38 **structure?**
09:52:39 A. **Okay. So if we go to Column 3 --**
09:52:41 Q. **And, Dr. Walensky, you are at JTX-38.3; is that**
09:52:44 **correct?**
09:52:44 A. **Yes. I'm at Column 3 and I'm going all the way to the**
09:52:47 **bottom of 65, just to point out that that is a peptide of**
09:52:50 **the formula where here, the N-terminal position is called an**
09:52:56 **N. And then we can go on and read what N is.**
09:53:00 **So N is a hydrogen atom -- now I'm up to the top**
09:53:04 **of Column 4. N is a hydrogen atom or a single acidic, basic**
09:53:12 **or neutral aromatic amino acid residue of the D- or L-**
09:53:18 **configuration such as D-Arg, D-Lys, or L-Thi, an N-terminal**
09:53:22 **enzyme protecting group selected from the group comprising**
09:53:25 **acyl-type protecting groups, aromatic urethane-type**
09:53:30 **protecting groups, alkyl-type protecting groups, or**

09:53:35 **alternately N is a di- or polypeptide containing amino acids of the D- or L-configuration, such as Lys-Lys, Met-Lys, or Gly-Arg-Met-Lys.**

09:53:40 **The language should be very familiar now. It lists n-terminus protecting groups to include acyl type protecting groups, which is a way to characterize all of those Z groups that I discussed, and it even includes the aromatic urethane option, which is when you combine that O with the C double bond, the green and the purple that I showed you. That's called urethane. It's even including the aromatic urethane type, which is Fmoc.**

09:54:05 Q. **Dr. Walensky, as of January 1989, would a POSA who was creating a bradykinin antagonist have wanted to add a protective barrier to enzymatic degradation?**

09:54:16 A. **Yes.**

09:54:17 Q. **If we would refer back to your earlier testimony, you said that the acyl groups and aromatic urethane groups are components of the Z group; is that correct?**

09:54:27 A. **Yes.**

09:54:28 Q. **You state on PDX-3.15 that at JTX-38.7 and 8, and that's Columns 12, lines 1 through 3, and column 13, line 16 through 19, that there are included examples of N-terminally modified bradykinin antagonists.**

09:54:48 **Could you discuss those examples, point them out and discuss them and how they inform your opinion?**

09:54:56 A. **Yes. So very briefly, I just wanted to show there are**
09:54:59 **examples in this list of peptides that have acyl groups. 42**
09:55:03 **has an acetyl group. 52 has an acetyl group. 56 has an**
09:55:10 **acetyl group.**
09:55:11 Q. **You also said there were biological implications of**
09:55:15 **the '963 patent, and if you could inform us as to how those**
09:55:19 **biological implications also informed your opinion.**
09:55:23 A. **Yes. So if you go over to Column 5, Table 2, and**
09:55:28 **there's a little arrow to N and then it tells you why we**
09:55:33 **have an N here. That's Column 5, JTX-38.4. There you go.**
09:55:44 **So if you look under N, it says, additions**
09:55:48 **confer enzyme resistance.**
09:55:59 Q. **And, Dr. Walensky, if you could turn to Table 5 on**
09:56:03 **JTX-38.10 to 11. And how would the data in Table 5 at all**
09:56:11 **inform a POSA about the N-terminal modifications of a**
09:56:15 **bradykinin antagonist?**
09:56:16 A. **So if you look at -- let's highlight Examples 51 and**
09:56:22 **52. This is a data table telling about biological activity**
09:56:28 **of peptides, which is bradykinin antagonist blood pressure**
09:56:32 **assays. I just want to mention, if you can just highlight**
09:56:35 **in the legend at the bottom just to define what Roman**
09:56:39 **Numeral I-B is. That's just an indicator of bradykinin**
09:56:43 **antagonistic activity. So that's what you are looking for**
09:56:46 **in this table. If you see that, that means you got what you**
09:56:48 **want.**

09:56:49 **So we're looking at Examples 51 and 52. They're very comparable examples because 51 does not have the N-acetyl group, doesn't have the N protection and 52 does. Now, let's look at the results.**

09:57:02 **When you don't have the acetyl group, do you have antagonist activity? No. At the interarterial? No. IV, do you have antagonist activity, next column? No. If you go to the destruction column, how much destruction do you have? 52 percent destruction.**

09:57:21 **So now you go to 52. You say what happens to that bad profile when I add an acetyl? All of a sudden I've added just acetyl group and I get what antagonist activity.**

09:57:36 **Do I get antagonist activity? All of a sudden I do. How about destruction? Do I have destruction anymore? No, I don't. So all they did was add this acetyl group to the identical peptide in this example, and they've gone from an agonist that gets destroyed to an antagonist that doesn't.**

09:57:53 **And that's not a one hit wonder, because I can show you the exact same thing. I won't go through it all again. But 55 and 56 is the identical scenario. 55, no N-terminal permanent acetyl group. 56, N-terminal permanent acetyl group. We go from a peptide that's an agonist that gets destroyed to exactly what we want, bradykinin antagonist that does not just by adding that N-terminal**

09:58:21 **modification.**

09:58:21 **Q. Dr. Walensky, you also relied on the kinin antagonist**
09:58:26 **article, which is JTX-39 for your opinion that a POSA would**
09:58:31 **not have been motivated to remove an N-terminal modification**
09:58:34 **of a peptide of Claim 1 of the '7,803 patent.**

09:58:37 **Could you briefly describe for us how that**
09:58:41 **article, JTX 39, informs your opinion?**

09:58:43 **A. Yes. And I just want to keep reminding in my answer**
09:58:47 **that the reason why I'm going through all of this is because**
09:58:51 **Dr. Bachovchin said you see that group, you take it off.**
09:58:53 **You see that group, you take it off. Well, I'm trying to**
09:58:56 **give examples from the literature prior to January of 1989**
09:59:00 **where there were explicit reasons not to take it off, so I**
09:59:03 **gave you my first one, which was this patent that showed you**
09:59:06 **put an acetyl group on the N-terminus, you get some great**
09:59:09 **antagonist activity. Now I'm going to give you another**
09:59:12 **example in a completely different setting.**

09:59:13 **So in this paper they talk about, let's go to**
09:59:16 **the last, let's go to JTX-39.11. You go to the last**
09:59:20 **paragraph. It says, recent studies, reviewed by Regoli,**
09:59:25 **have shown that some B2 receptor antagonists are very active**
09:59:29 **histamine releasers. So that's a bad thing. You don't want**
09:59:33 **that.**

09:59:34 **But this effect -- that's a side effect. You**
09:59:36 **have histamine release from your treatment, that's a bad**

09:59:39 **side effect, so you don't want it. But this side effect can**
09:59:44 **be reduced or eliminated by acetylation of the N-terminal**
09:59:48 **amide.**
09:59:49 **Now, here's another reason why you would keep it**
09:59:51 **on. In a totally different scenario, you would want to keep**
09:59:55 **that N-terminal acetyl group on. Why? Because you**
09:59:58 **eliminate a side effect, a bad side effect, which is**
10:00:01 **histamine release.**
10:00:02 **Now let's read on. Those compounds maintain**
10:00:04 **agonistic effect. Okay. So these were not antagonists and**
10:00:09 **they promote catecholamine release. These compounds have**
10:00:15 **other problems with them.**
10:00:17 **However, here's the story of peptide synthesis.**
10:00:19 **Having agonistic activity is, however, reduced by the**
10:00:22 **addition of a D-Arg at the N-terminal and by the replacement**
10:00:28 **of Pro by hydroxyproline.**
10:00:31 **So this is your very typical scenario where you**
10:00:34 **do something over here on one side and it helps you but it**
10:00:37 **may not fix everything, but you don't get rid of this, which**
10:00:40 **is doing something for you, and you just change a little bit**
10:00:42 **of this and a little bit of this, because you have all these**
10:00:45 **different positions in peptides to play around with to get**
10:00:47 **to where you want to go.**
10:00:48 **So this is an example where they got rid of a**
10:00:51 **side effect that they didn't want by sticking an acetyl**

10:00:55 **group over here at the N-terminus. Didn't fix all of their**
10:00:58 **problems, but it fixed an important one, and then they fixed**
10:01:02 **others by making important changes. This is where making an**
10:01:05 **N-terminal modification got rid of a side effect.**
10:01:08 Q. **Doctor, you also identify Table 5 in the kinin**
10:01:11 **antagonist article. Could you describe how that table**
10:01:15 **informed your opinion with respect to not removing**
10:01:18 **N-terminal modification?**
10:01:19 A. **Right. So this is just kind of more of the same here.**
10:01:22 **I'm trying to pick out comparable examples. So if you look**
10:01:24 **at Example 4 and 5, if you can highlight that, these are two**
10:01:28 **peptides that are -- there you go, and then the one right**
10:01:32 **below it.**
10:01:34 **So what you are seeing here is by adding on that**
10:01:37 **acetyl group, you essentially maintain the activity of the**
10:01:40 **peptide. Right. So you can get rid of a side effect and**
10:01:43 **maintain the biological activity, that you want, and then**
10:01:46 **there's another example of that directly below.**
10:01:49 **So if you look at six and seven there, so**
10:01:51 **there's an example of a peptide that has a D-Arg at the**
10:01:57 **N-terminus, and then the one below that has an acyl group**
10:02:01 **added on top of the D-Arg. And the activity in these assays**
10:02:07 **are essentially the same, but you get the added benefit of**
10:02:11 **not having the undesirable histamine release.**
10:02:15 Q. **Dr. Walensky, you also relied on the '204 patent**

10:02:19 **in the prior art to inform your opinion as why the POSA**
10:02:23 **would not be motivated to remove the N-terminal modification**
10:02:27 **in the peptides of Claim 1 of the 7,803 patent. And how**
10:02:31 **did the '204 patent inform your opinion? And that is**
10:02:36 **JTX-40.**
10:02:37 A. **Okay. So I'm going to Column 3 and I'm starting at**
10:02:51 **the very top of the column there.**
10:02:53 **So this really reinforces the schematic and**
10:02:58 **the language of the method of synthesis in '7,803. Let me**
10:03:02 **read.**
10:03:02 **The term N protecting group -- again, we're**
10:03:04 **talking about that N-terminal protecting group -- as used**
10:03:07 **herein, refers to those groups intended to protect the**
10:03:10 **N-terminus against undesirable reactions, emphasis added,**
10:03:15 **during synthetic procedures.**
10:03:18 **Okay. So that part of the sentence refers to**
10:03:20 **the green functionality of Fmoc, on/off, on/off, on/off.**
10:03:25 **Okay. Now we go, or -- so now we're talking about something**
10:03:30 **different, or to prevent the attack of exopeptidases on the**
10:03:34 **final compounds or to increase the solubility of the final**
10:03:37 **compounds.**
10:03:41 **Okay. It toggles you down to the second half of**
10:03:44 **that slide, where we're talking about the purple function,**
10:03:48 **the permanent function of the Fmocs, and it gives two**
10:03:51 **examples of why that's useful here, and then it lists some**

10:03:57 choices. Including, but not limited to, acyl, which is what
10:03:59 we've been talking about all morning, acetyl, which I just
10:04:02 gave you an example of, and it goes on. Pivaloyl,
10:04:07 T-butyloxycarbonyl. Can come on and off and on and off
10:04:14 during synthesis, but when it's left on for a reason, it
10:04:17 stays on as part of the final product. It lists that.
10:04:24 Carbobenzyloxycarbonyl or benzoyl groups. You may remember
10:04:25 that benzoyl group was stated as one of the Z group options
10:04:29 as well or an L or D aminoacyl residue. An example of that
10:04:33 one would be like D-arginine, which may itself be N
10:04:37 protected similarly.
10:04:38 Here they are saying you can add a D-arginine
10:04:41 type amino acid there and you can protect it, too. We just
10:04:45 saw an example of that in the article in Example 7 where
10:04:48 they had that D-arginine at the position and then they stuck
10:04:51 an acetyl group on it as well, and that's exactly what it
10:04:54 says here as a recommendation for having an N protected
10:04:57 group that might prevent the attack of exopeptidase.
10:05:01 Q. And finally, Dr. Walensky, you had a fourth piece of
10:05:04 prior art that you relied on to explain why a person of
10:05:07 ordinary skill in the art wouldn't be motivated to remove
10:05:10 the N-terminal modification, and that is JTX-15.
10:05:14 If we could turn to JTX-15, Dr. Walensky, and
10:05:18 would you please describe and explain why you relied on
10:05:22 JTX-15 for your opinion.

10:05:24 A. **So if you go to JTX-15.31, the last paragraph on the**
10:05:30 **page. It says, several simple amine protecting groups**
10:05:35 **derived from carboxylic acids and commonly used in organic**
10:05:39 **synthesis are obviously not suitable in peptide synthesis.**
10:05:46 **And then they go on to give an example. Emphasize the term**
10:05:50 **obvious.**
10:05:50 **For instance, acetylation or benzoylation, both**
10:05:56 **Z examples in the '7,803. These groups are, what does it**
10:06:01 **say? Impractical, and then it gives an explanation, because**
10:06:04 **the vigorous hydrolysis needed for deacylation cleaves**
10:06:09 **peptide bonds as well.**
10:06:13 **This speaks to permanence. When you put on a**
10:06:15 **group that's a Z group, an acetyl group, a benzoyl group or**
10:06:20 **an Fmoc group or Boc group and your goal is to leave it on**
10:06:24 **there, you don't take it off.**
10:06:25 **Okay. And if you put on ten out of eleven of**
10:06:28 **those Z groups, do you know what this says? If you went on**
10:06:31 **and tried to take it off, you've destroyed the whole**
10:06:33 **peptide. A person of ordinary skill in the art would know**
10:06:36 **without any question that when you put these Z groups on**
10:06:39 **there, they don't come off after the fact, because if you**
10:06:42 **took it off after the fact, what does it say here? Cleaves**
10:06:45 **the peptide bonds as well. That means destroy the peptide.**
10:06:52 **That's pretty clear.**
10:06:53 Q. **Dr. Walensky, if we could turn back, all the way back**

10:06:59 **now to PDX-3.6. You also stated, you had a broader opinion**
10:07:04 **there, your third point.**
10:07:06 **You state that as of January 1989, a POSA**
10:07:08 **confronted with D-Tic at position seven and Oic at position**
10:07:13 **eight in the context of a peptide that otherwise appears to**
10:07:16 **be a bradykinin analog would have had no reasonable**
10:07:19 **expectation of success that such a peptide would have**
10:07:22 **bradykinin antagonist activity.**
10:07:24 **I'd like to talk about position seven first, and**
10:07:28 **what are your bases for this opinion?**
10:07:30 A. **So I summarized that on PDX--3.16. If we can go to**
10:07:36 **that. The reasons are, first, the literature did not teach**
10:07:40 **or suggest the use of the unnatural, conformationally**
10:07:43 **constrained amino acid Tic in any position of a bradykinin**
10:07:46 **antagonist.**
10:07:47 **The second point is that the literature did not**
10:07:49 **teach or suggest the use of a conformationally constrained**
10:07:53 **bycyclic amino acid like Tic in any position of a bradykinin**
10:07:56 **antagonist.**
10:07:57 **The third point is that the literature did not**
10:08:00 **teach or suggest the use of Tic to address the metabolic**
10:08:03 **instabililty of a bradykinin antagonist.**
10:08:05 **Four, not all D-aromatic amino acids at position**
10:08:09 **seven conferred bradykinin antagonist activity.**
10:08:13 **So a POSA confronted with D-Tic at position**

10:08:18 **seven in the context of a peptide that otherwise appears to**
10:08:21 **be a bradykinin analog, would have been motivated to**
10:08:23 **substitute the D amino acids expressly suggested in the**
10:08:26 **bradykinin literature for use at position seven to create a**
10:08:30 **bradykinin antagonist.**
10:08:32 Q. **On PDX-3.16, you referred to conformationally**
10:08:37 **constrained. What do you mean by conformationally**
10:08:39 **constrained?**
10:08:40 A. **So what I mean by conformationally constrained, first,**
10:08:44 **I will start with the word "conformation." Chemistry is a**
10:08:46 **three-dimensional art. We talk about everything on a**
10:08:49 **two-dimensional plane, but this is a three-dimensional**
10:08:51 **science, and to add the other level of complexity, it's a**
10:08:54 **three-dimensional moving science.**
10:08:56 **So we're dealing with things that are**
10:08:57 **three-dimensional, and they're constantly moving and**
10:09:00 **spinning, and all -- they consume space, real space. So**
10:09:04 **that's what I mean by conformation.**
10:09:07 **And so if we go to PDX--3.17, I could just**
10:09:11 **elaborate on this because I made a schematic that I think is**
10:09:15 **also critical.**
10:09:32 **I title my slide The Critical Difference Between**
10:09:34 **a Non-Constrained and a Constrained Amino Acid Side Chain.**
10:09:39 **What we are talking about here is the difference**
10:09:42 **between the D-phenylalanine and D-Tic. We heard on Monday**

10:09:47 **that these things look the same. You just look at them, and**
10:09:52 **they look the same. These are two-dimensional depictions by**
10:09:56 **a chemistry drawing program that simplifies what these two**
10:10:01 **amino acids look like.**
10:10:05 **That is the beginning. These are not**
10:10:07 **two-dimensional compounds that are sticks. These are**
10:10:10 **three-dimensional entities.**
10:10:12 **Just because they on a very superficial level,**
10:10:16 **quote-unquote, look the same, I want to explain to you how**
10:10:20 **not the same they really are.**
10:10:21 **First, let's continue with two-dimensional**
10:10:24 **space. Just by looking at them in two-dimensional space,**
10:10:28 **what you see here is D-Phe is a monocyclic system. It is**
10:10:31 **one ring. D-Tic is a bicyclic system. That is two rings.**
10:10:35 **That is one difference.**
10:10:36 **Another difference. D-Phe is a homocyclic ring.**
10:10:40 **That means every atom there is a carbon. The main atom is a**
10:10:44 **carbon with some hydrogens.**
10:10:46 **D-Tic is heterocyclic, carbons, hydrogens, and**
10:10:50 **now you have also added in a different atom, nitrogen.**
10:10:55 **What I am going to talk about now,**
10:10:56 **D-phenylalanine is not constrained and D-Tic is**
10:11:00 **conformationally constrained. What does that mean and why**
10:11:03 **do we care?**
10:11:04 **Okay. Okay. Let's start with D-phenylalanine.**

10:11:08 **D-phenylalanine in three-dimensional space as a moving**
10:11:13 **entity spins. So those arrows are meant to detect spinning.**
10:11:16 **Let's make the analogy between a propeller on an**
10:11:20 **airplane. So this thing can spin around like a propeller on**
10:11:23 **an airplane. Why does that matter?**
10:11:25 **If you go to the next panel, when a peptide is**
10:11:27 **trying to bind to its target, if that thing is spinning like**
10:11:31 **a propeller on an airplane, what that means is it can adopt**
10:11:36 **innumerable conformations. It can sample so many different**
10:11:40 **three-dimensional conformations in space until it finds just**
10:11:43 **the right one to fit into that receptor and it uses that**
10:11:47 **conformation and binds.**
10:11:49 **Let's go to the bottom.**
10:11:51 **Conformationally constrained means that now we**
10:11:54 **have added a methylene group that I have highlighted in**
10:11:57 **yellow, that CH-2 group that we have been discussing. What**
10:12:00 **does that do?**
10:12:01 **That conformationally constrains the propeller.**
10:12:05 **So when you think about that as an airplane, yeah, it's**
10:12:08 **still a propeller, it's not the exact type of propeller,**
10:12:13 **what is the biggest difference? It doesn't move very much.**
10:12:15 **That plane is not taking off. That cannot spin on its axis.**
10:12:19 **That is a conformationally constrained amino acid. Why do**
10:12:22 **we care?**
10:12:24 **Now think about what that peptide has to do to**

10:12:26 **bind to its receptor. If you go to the next panel, now,**
10:12:29 **this peptide has very much reduced choices for how it can**
10:12:34 **interact with the receptor. And if that's not the perfect**
10:12:38 **choice, then that peptide is in no way going to bind to that**
10:12:42 **receptor.**
10:12:43 **So you have gone from the ability to choose from**
10:12:46 **an innumerable number of conformations to completely**
10:12:50 **restrict your ability to move around in space,**
10:12:53 **conformationally constrained. And a huge risk factor in**
10:12:57 **doing that is you may never find the right shape to fit into**
10:13:02 **that receptor because you are so limited in your ability to**
10:13:05 **move.**
10:13:06 **I want to summarize my point. Conformational**
10:13:08 **constraint in three-dimensional space, where movement and**
10:13:11 **space occupation is critical to drug design, that is, I**
10:13:15 **cannot under-emphasize how big a difference that is, even**
10:13:18 **though, if you wanted to be oversimplifying, you can just**
10:13:22 **say, oh, yes, those two shapes, they kind of look the same.**
10:13:25 **A POSA knows better.**
10:13:28 Q. **Dr. Walensky, moving on with regard to your opinions**
10:13:33 **Position 7 and D-Tic, you also stated that all the aromatic**
10:13:38 **amino acids at Position 7 don't confer bradykinin antagonist**
10:13:43 **activity. What is the basis for that? Again, that was on**
10:13:50 **your PDX3.16.**
10:13:54 A. **You are going back.**

10:13:55 Q. **You identified that point on 3.16.**

10:13:59 A. **Yes. If you go to the bottom there, what I wanted to discuss is the concept that, the notion that not all D-aromatic amino acids at Position 7 actually even confer greater bradykinin antagonistic action. And I wanted to go to JTX-25 to point that out.**

10:14:22 **If you go to JTX-25, this is the breakthrough article. This was the Vavrek and Stewart article from 1985 that made the first discovery of making the first bradykinin antagonist. In the abstract I wanted to point out when they replaced the proline residue at Position 7 of bradykinin with D-phenylalanine, that was the conversion that converted the BK agonist into the bradykinin antagonist.**

10:14:49 **This was really the beginning of the beginning of this bradykinin antagonist field.**

10:14:54 **If you turn to Table 1, the point to be made here is that that change was a needle in a haystack. It was an exception to the rule.**

10:15:04 **What makes me have that opinion? If you go to Table 1, and you look at all of the choices there, and there is a lot of choices for D-amino acids, and there is also a lot of choices for D-aromatic amino acids, the only choice that had antagonistic action was one of the D-aromatic amino acids that is listed there. All the other choices do not work.**

10:15:31 **So to over-generalize and say, yep, it's a**
10:15:34 **D-aromatic acid replacement, pick whichever one you want,**
10:15:38 **absolutely not. D-phenylalanine in this table is the**
10:15:42 **exception to this rule. It is the needle in the haystack.**
10:15:46 **And that's why this was such a big discovery.**
10:15:48 Q. **Dr. Walensky, your last opinion on PDX-3.16 states**
10:15:52 **that a POSA when confronted with a D-Tic in Position 7 in**
10:15:58 **the context of a peptide which appears to be a bradykinin**
10:16:01 **analog would have been motivated to substitute the D-amino**
10:16:05 **acid expressly suggested in the bradykinin literature.**
10:16:08 **What literature did you rely on for this**
10:16:10 **opinion?**
10:16:11 A. **If you go to PDX-3.18, I just list here the patents**
10:16:16 **that I referred to in the prior art, '963, '993, '613, this**
10:16:23 **is what I am relying on to show you that a POSA would have**
10:16:26 **substituted D-amino acids at Position 7 from among these**
10:16:29 **choices that we can go through.**
10:16:31 Q. **If we can take a look at your first document that you**
10:16:34 **identify, JTX-28. If you could identify on JTX-28 what you**
10:16:40 **are relying on for this opinion?**
10:16:43 A. **In the interests of time, I basically put the relevant**
10:16:45 **parts on slides so we don't have to keep going back and**
10:16:48 **forth and highlighting and whatnot.**
10:16:49 **On PDX-3.19, in this patent, the 7 position is**
10:16:54 **called Y. On the left are all the choices that these**

10:16:57 **inventors gave you for Y. And then in the table on the**
10:17:00 **right, they give you their favorite choices that are**
10:17:02 **highlighted in yellow.**
10:17:04 Q. **So, Dr. Walensky, you also identified the U.S. Patent**
10:17:10 **4,801,613. And if you could then explain for us what you**
10:17:18 **relied on in that patent for your opinion?**
10:17:20 A. **Same concept, PDX-3.20 here, here the formula is**
10:17:23 **shown, and again, Y is what they are calling 7 and they list**
10:17:27 **a whole bunch of amino acid choices for what you could**
10:17:30 **substitute in there at Position 7.**
10:17:32 Q. **And so finally, you have the '963 patent that you are**
10:17:36 **relying on, JTX-38, for your opinion as to what would be**
10:17:41 **substituted at Position 7. Could you just summarize that**
10:17:43 **for us?**
10:17:44 A. **Yes. Same situation. PDX-3.21, yellow lists all the**
10:17:50 **different choice possibilities here. And then again these**
10:17:53 **are Y choices, that is a different letter, but it is the**
10:17:55 **same position, No. 7.**
10:17:57 **If you actually turn to PDX-3.22, I just put**
10:18:00 **this all together, summarized it. If you look at the**
10:18:03 **patents here, in the prior art, these are all the different**
10:18:08 **possible choices that were listed in these patents for what**
10:18:11 **you could do in substitution at Position 7. Then the**
10:18:15 **asterisks are some preferred choices.**
10:18:17 **So this is kind of the whole menu. In the '613**

10:18:20 and '963 columns I didn't repeat everything from the first
10:18:24 column. I just showed the new ones that were gleaned from
10:18:27 those two patents.
10:18:28 Q. Thank you, Dr. Walensky.
10:18:32 In consideration of time, you also provided an
10:18:34 opinion as to, with respect to Position 8. You state that a
10:18:39 person of ordinary skill in the art confronted with a
10:18:42 bradykinin analog with D-Tic at 7 and Oic at 8 would have
10:18:50 substituted the Oic with recommended amino acids in the
10:18:54 bradykinin literature. Is that correct?
10:18:56 A. That's right. So my reasons for saying that a POSA
10:18:58 would not have kept Oic at Position 8 are as follows.
10:19:02 The literature did not teach or suggest the use
10:19:05 of the unnatural conformationally constrained amino acid Oic
10:19:08 in any position of a bradykinin antagonist. The literature,
10:19:12 No. 2, did not teach or suggest the use of a
10:19:14 conformationally constrained bicyclic amino acid like Oic in
10:19:20 any position of a bradykinin antagonist.
10:19:24 Third, the literature did not teach or suggest
10:19:26 the use of Oic to address the problem of metabolic
instability for a bradykinin antagonist.
10:19:31 Fourth, the literature did not teach or suggest
10:19:33 that the use of Oic in a peptide necessarily results in the
10:19:37 desired biological activity.
10:19:38 Finally, a POSA faced with a bradykinin analog

10:19:42 **with D-Tic at Position 7 and Oic at Position 8 as of January**
10:19:47 **1989 would have been motivated to substitute the amino acids**
10:19:50 **expressly suggested in the bradykinin literature for**
10:19:53 **Position 8 to create a bradykinin antagonist.**
10:19:57 **Q. Dr. Walensky, let's go right to your identification of**
10:20:02 **DTX-114.**
10:20:05 **You say that source indicates that the**
10:20:07 **literature did not teach or suggest the use of a**
10:20:09 **conformationally constrained bicyclic amino acid. What are**
10:20:12 **you relying on in DTX-114?**
10:20:15 **A. I summarize what I have relied on in PDX-3.24.**
10:20:19 **First, the information in this article, which is**
10:20:21 **titled The Inhibition of Glandular Kallikrein by Peptide**
10:20:26 **Analog Antagonists of Bradykinin, the author is Spragg.**
10:20:33 **Regarding Position 8 a bradykinin antagonist is limited to**
10:20:33 **amino acids that were not conformationally constrained, and**
10:20:37 **therefore could not teach or suggest anything about the**
10:20:39 **impact of the conformationally constrained amino acid like**
10:20:44 **Oic at Position 8 when designing a bradykinin antagonist.**
10:20:48 **That is No. 1.**
10:20:49 **No. 2 is that Spragg is not directed at**
10:20:52 **developing a bradykinin antagonist that binds to the**
10:20:56 **bradykinin receptor. Instead, Spragg talks about bradykinin**
10:20:59 **antagonists that are evaluated for their ability to inhibit**
10:21:02 **kallikreins. Information related to design of an inhibitor**

10:21:05 **of a kallikrein, which is a protease that acts on a high**
10:21:09 **molecular weight kininogen and its pathway, kallikrein-kinin**
10:21:16 **system, would not have informed a POSA on how to design a**
10:21:19 **bradykinin antagonist that must interact with the bradykinin**
10:21:24 **receptor.**

10:21:24 **To keep that very simple, if you were designing**
10:21:26 **a key to open a lock, if I am locked out of my house and I**
10:21:30 **call a locksmith to open my front door, I don't send them to**
10:21:34 **the neighbor. What he learns about the lock on my**
10:21:37 **neighbor's front door has nothing to do with the lock on my**
10:21:40 **front door.**

10:21:41 **So if you are trying to glean information about**
10:21:43 **how to come up with a bradykinin antagonist, you don't go to**
10:21:47 **the neighbor kallikrein, who has a different receptor with a**
10:21:52 **different function, and ask him to make a lock for that.**
10:21:56 **That is not going to open my front door.**

10:21:58 **It may open his but not mine. I am still going**
10:22:02 **to be locked out.**

10:22:02 Q. **You said that Position 8 in the literature in Spragg**
10:22:06 **is limited to amino acids that were not conformationally**
10:22:09 **constrained?**

10:22:09 A. **Yes.**

10:22:10 Q. **What is your support for that?**

10:22:12 A. **If you go to Spragg, DTX-114, Page 7, which in the**
10:22:18 **Spragg article is 205 in the upper right there, let's just**

10:22:22 read from substitution, which is the upper right column.

10:22:27 Substitution at the P2 position with bulky
10:22:31 analogs such as cyclohexylalanine indicates that minimal
10:22:36 steric restraints are observed at this position. The
10:22:38 bradykinin analog antagonists examined here contain
10:22:42 substitutions that meet these steric criteria at Positions
10:22:45 P1 to P3. Namely, they have L-Arginine at P1,
10:22:50 L-phenylalanine or Beta-2-thienyl-L-alanine at P2, and
10:22:56 D-phenylalanine at P3.

10:22:57 The numbers and naming is unfortunately
10:23:00 different. If you zoom up to the table, P2 in this table is
10:23:03 the 8 position.

10:23:05 The only choices that are discussed in this
10:23:07 article are listed in P2. They are talking about
10:23:11 phenylalanine, thienylalanine, in the section I just told
10:23:16 you, read to you, they talk about cyclohexylalanine as well.
10:23:21 None of these are conformationally constrained.

10:23:23 Why does that matter? I kind of prepared a
10:23:26 simplified slide like I did before to explain why this is so
10:23:30 important and why this article does not speak at all to
10:23:34 conformational constraint.

10:23:34 This is by analogy what I showed before with the
10:23:37 spinning propellers. PDX-3.25.

10:23:40 On the left are the amino acids that are
10:23:42 described in Spragg. Phenylalanine, which we already beat

10:23:46 **the dead horse on, that is a non-conformationally**
10:23:49 **constrained amino acid. It spins on its axis.**
10:23:52 **Spragg also talks about cyclohexylalanine. That**
10:23:55 **also spins. Then it talks about beta-2-thienylalanine.**
10:24:00 **That also spins. This paper does not talk at all about Oic.**
10:24:03 **But if we want to talk about Oic, let's see how those three**
10:24:07 **things compare to Oic.**
10:24:09 **Oic is on the right. So Oic is a bicyclic ring**
10:24:12 **system. Nothing on the left is bicyclic.**
10:24:15 **What is different about Oic? It does not spin.**
10:24:17 **It's conformationally constrained. Completely different.**
10:24:20 **So you can argue that the only difference between this one**
10:24:24 **on the right, it kind of looks like one of them on the left.**
10:24:27 **You can say, does that look like cyclohexylalanine in two**
10:24:31 **dimensions? Sure.**
10:24:32 **You can say the chemical structure of these two**
10:24:34 **things kind of look the same. Is that the level of a POSA,**
10:24:37 **is that the level of sophistication that we are talking**
10:24:39 **about in drug development? Of course not. The**
10:24:41 **sophistication is we are making three-dimensional drugs for**
10:24:44 **three-dimensional targets. Everything on the left spins.**
10:24:47 **The compound on the right Oic is conformationally**
10:24:50 **constrained. That is a completely different function and**
10:24:52 **role in the design of a drug.**
10:24:56 **To say that those Spragg compounds inform the**

10:24:58 choice of Oic is just, in my opinion, completely wrong.
10:25:04 Q. Dr. Walensky, at PDX-3.23, you said that the
10:25:09 literature didn't teach or suggest the use of Oic in a
10:25:12 peptide necessarily results in the desired biological
10:25:16 activity and you referred to DTX-58?
10:25:24 A. This is Blankley?
10:25:26 Q. Yes.
10:25:26 A. So I summarized my thoughts about Blankley, 3.26.
10:25:32 Blankley is an article that is titled Synthesis and
10:25:35 Structure-Activity Relationships of Potent New Angiotensin
10:25:39 Converting Enzyme Inhibitors Containing Saturated Bicyclic
10:25:42 Amino Acids.
10:25:44 First I want to point out again, my locksmith is
10:25:46 at the neighbor's front door. We are not working on the
10:25:49 relevant lock here.
10:25:50 Be that as it may, let's continue.
10:25:53 Blankley contains in vitro and in vivo icatibant
10:25:56 comparing ACE inhibitors with proline versus a series of ACE
10:26:00 inhibitors containing bicyclic amino acids in place of
10:26:02 proline.
10:26:03 What we are doing here is comparing compounds
10:26:05 that have a proline versus ones that have a bicyclic
10:26:08 conformationally constrained structure.
10:26:15 Q. Dr. Walensky, if you could move on to your examples of
10:26:18 the in vitro and in-vivo data that you used to support your

10:26:22 **opinion?**

10:26:22 A. **Sure.**

10:26:23 **In PDX-3.27, there is a whole lot of constructs**
10:26:27 **and a whole lot of data in this paper. I am going to try to**
10:26:30 **go through it quickly but make the key points.**

10:26:32 **In Table 1, this is in-vitro data. If you look**
10:26:35 **at the top row, there is a whole bunch of different**
10:26:38 **structures. One of those is Oic. Oic is, under the column**
10:26:41 **that says X, you will see that there is a bunch of A's.**
10:26:44 **Those A's mean Oic.**

10:26:47 **Everything that I have highlighted in yellow are**
10:26:50 **Oic-containing compounds. What we are doing here is we are**
10:26:53 **comparing them to the drug, which is captopril. It is a**
10:26:58 **blood pressure lowering drug.**

10:26:59 **I took one this morning.**

10:27:02 **So 1A is captopril. And so we are trying to do**
10:27:06 **better. We are trying to look at ways to do better.**

10:27:09 **If you look at all the Oic compounds and their**
10:27:12 **biological results, I think it is safe to say that those**
10:27:14 **results are all over the park.**

10:27:16 **Some are barely better. Some are no better.**
10:27:19 **And some are worse.**

10:27:20 **A POSA looking at that and saying let me see how**
10:27:23 **those Oic substitutions do, they walk away from that saying,**
10:27:27 **Who knows?**

10:27:28 **Now, if you want to be as fair as you possibly could be, you want to compare the compound that is as close in structure to captopril as you possibly can from that grab bag of compounds, if you do that, which is scientifically precise, I would pick 9f. The only difference in my opinion between 9f and captopril is the difference of Oic versus proline.**

10:27:52 **What do you see? You see that the Oic-containing compound is around 2.3 times better than captopril.**

10:28:02 **If I am a drug designer, I am not jumping off my seat, but it's a little better. So now we continue.**

10:28:11 **On the next table -- we keep going on. We keep doing this. Again in yellow are all the Oic compounds. Here we are comparing it to another drug, enalaprilat. If you look at the yellow compounds, same story, all over the park. Here actually nothing is better. Not one Oic-containing compound is better.**

10:28:30 **And they are all over the place. Some are barely not better. Some are totally not better. Some are unmeasurably poor, greater than a hundred. So if you make the fair comparison again, the most scientifically precise comparison is 11B to enalaprilat. .0023 is your goalpost. You are barely there at .0024. You don't make it. You are not even the same. You are a tad worse.**

10:28:56 **For all intents and purposes, it's the same.**

10:28:59 **Now let's look at the next one, 3.29. Now we are getting a little bit more sophisticated because we are going in vivo. One might argue that in vivo is important, because that is where you are injecting this thing into a mammal.**

10:29:12 **The fairest comparison that you can make in this table, and you really have to find that, because there is not a lot of head-to-heads, the only one I could find here is 9f at a dose of 30 milligrams per kilogram orally versus captopril, which was given at the same dose. Again, the only difference between those two things are Oic and proline.**

10:29:34 **We are trying to be convinced that, you see proline, let's just hit away, that is the home run. Well, here, what you are reading out is the maximum change in lowering the blood pressure. Captopril does minus 101 at six hours. See that? And 9f does minus 72. So in this assay the lower the number, the more you lower blood pressure, the better you do, and Oic does way worse.**

10:29:47 **So a POSA that looked at this data taken together to summarize it, they would see a whole bunch of compounds. There would be one out of all of these compounds that was a tad better, two, three times better, all the other ones were all over the park and the in vitro data in**

10:30:04 the other table. There isn't any of them that's better.
10:30:07 And then when you go to the in vivo data, the Oic
10:30:10 substitution makes it worse. So what does a POSA say? No,
10:30:14 thanks.
10:30:15 Q. Dr. Walensky, moving on, we're in the home stretch
10:30:21 here. You said on PDX-3.23 that as of January 1989, a POSA
10:30:28 would have been motivated to substitute in position eight
10:30:30 where Oic would be the amino acids that had been recommended
10:30:35 for position eight.
10:30:37 And if you could summarize your opinion there
10:30:39 and the information specifically that you relied on.
10:30:42 A. Right. So, again, this is going to go quickly because
10:30:46 I just want to show you the same type of thing I showed you
10:30:49 before. Two patents, '993, '963 gives a bunch of choices
10:30:54 for position eight, and we can go right through this.
10:30:57 If you look at 3.31, if you go to these
10:30:59 patents, position eight here is called Z. Bottom left
10:31:05 there, all of choices for position eight. Right-hand table,
10:31:10 the inventor's preferred choices for preferred compounds for
10:31:14 substitution at position eight.
10:31:15 You can go right to the next page, 3.32,
10:31:18 and move on to the '963 patent, the same situation. And
10:31:23 that patent, again, they call position 8, Z, and they say
10:31:26 that Z, which is position eight, is a phenylalanine residue
10:31:30 of the D or L configuration, or, and it lists the choice

10:31:34 of substitutes, other aromatic or aromatic amino acid
10:31:39 residues such as Leu, Thi, or Pal or a cyclic amino acid
such as D or L Pro.
10:31:46 And then I summarized those choices on
10:31:51 PDX-3.33 and these are the choices that the inventors
10:31:54 suggested could be substitutions for position eight.
10:31:57 Q. Doctor --
10:31:59 A. After these preferred choices, among the choices.
10:32:03 Q. Dr. Walensky, at the outset of the testimony, you
10:32:05 stated that you reached the opinion that Claim 14 of the
10:32:08 '333 patent is not invalid for obviousness-type double
10:32:12 patenting over Claim 1 of the '7,803 patent in view of the
10:32:16 prior art. Given your direct testimony today, could you
10:32:20 please summarize why your opinion, this is the case?
10:32:24 A. Sure. So I just listed my simple positions starting
10:32:27 at PDX-3.34 and I want to read them into the record.
10:32:30 The first one is, the language of Claim 1
10:32:32 of the '7,803 patent makes clear that the N-terminal
10:32:35 modifications represented by the Z group are permanent
10:32:40 components of the peptides, not to be removed, and there is
10:32:42 no option listed for not having a "Z" component.
10:32:45 Number two, the specification of the '7,803
10:32:51 patent confirms that the Z groups are an integral part of
10:32:53 the final peptide, not to be removed.
10:32:55 Three, the bradykinin antagonist literature

10:32:59 **expressly taught to put aromatic urethane-type groups like**
10:33:05 **Fmoc and acyl-type groups at the N-terminus of bradykinin**
10:33:08 **antagonists to improve metabolic stability or confer other**
10:33:12 **beneficial biological activity.**

10:33:15 **Number four, a POSA confronted with a bradykinin**
10:33:19 **analog having D-Tic at position seven and Oic at position**
10:33:23 **eight would have had no reasonable expectation of success**
10:33:26 **that this peptide would have bradykinin antagonist activity.**

10:33:32 **Five, not only would a POSA not have been able**
10:33:35 **to predict how one or more changes in the amino acid**
10:33:38 **sequence of a bradykinin analog would impact the antagonist**
10:33:42 **potency of a peptide, a POSA would have had no idea how that**
10:33:47 **change would impact other characteristics of the molecule**
10:33:51 **aside from potency, such as metabolic stability.**

10:33:55 **And to reinforce that point, I wanted to excerpt**
10:33:58 **straight from the horse's mouth the discoverer of the first**
10:34:03 **bradykinin antagonist, Stewart. This is what he said on**
10:34:06 **page PDX-3.36 from his article, which I think I referred to**
10:34:11 **Stewart 4. It is clear from examination of these analogs**
10:34:15 **that there is no correlation between bradykinin potency of**
10:34:19 **analogs and their susceptibility to pulmonary kininases.**
10:34:26 **Some of the totally resistant analogs have very high potency**
10:34:31 **while others have very low inherent potency. Substrate**
10:34:35 **specificity requirements for the kininases thus are totally**
10:34:40 **different from receptor binding requirements. Simply put,**

10:34:47 clearly said.

10:34:49 And finally, my point 6 on PDX-3.37. Based on
10:34:55 the explicit teachings of Dr. Stewart and the compilation of
10:34:59 prior art, a POSA would have known that the design
10:35:02 principles derived for targeting a particular receptor with
10:35:05 a peptide composition were generally not applicable for
10:35:09 developing a peptide to target a different receptor. For
10:35:13 example, introducing conformational constraint could
10:35:17 facilitate the binding of a peptide to a particular
10:35:20 receptor, but making the same change in a different
10:35:23 peptide could completely destroy the activity towards its
10:35:27 receptor.

10:35:30 And I don't want to end with my words, I want to
10:35:34 end with the discoverer's words. Stewart wrote, in Stewart
10:35:41 four, first paragraph. Extensive work on analogs of peptide
10:35:46 hormones over more than two decades has demonstrated clearly
10:35:50 that few generalizations can be made in this field. The
10:35:56 different hormones are very individualistic, and their
10:36:00 receptors demonstrate very different specificity
10:36:03 requirements. As a consequence, principles operating in the
10:36:08 design of inhibitors of the action of one peptide hormone
10:36:12 are generally not applicable to other peptide systems.

10:36:18 And then he gives an example, almost a prophetic
10:36:23 example for what we're talking about here. Replacement of
10:36:28 phenylalanine by N-methylphenylalanine in angiotensin 2,

10:36:37 **which is not a peptide we've been discussing, yielded an**
10:36:40 **excellent inhibitor. The conformational restriction imposed**
10:36:43 **upon the molecule by this methylation apparently prevented**
10:36:46 **the aromatic ring (which is the trigger for intrinsic**
10:36:49 **activity) from interacting properly with the receptor.**
10:36:54 **So what that says is that when they introduce**
10:36:56 **conformational constraint by changing the phenylalanine to a**
10:37:00 **conformationally restricted one, they got a home run on that**
10:37:03 **receptor. It worked beautifully. However, I will read on.**
10:37:08 **Similar replacement of phenylalanine in bradykinin, which is**
10:37:13 **what we're talking about, served only to destroy all**
10:37:17 **activity.**
10:37:20 **What was a good conformational constraint for**
10:37:23 **the neighbor's lock doesn't open my door. Addition of an**
10:37:28 **alpha methyl group to the phenylalanine, this was a**
10:37:32 **different style of introducing conformational constraint,**
10:37:34 **which also severely restricts the conformational flexibility**
10:37:38 **of the molecule, had a much less deleterious effect than the**
10:37:43 **other inhibitor above.**
10:37:45 **What happened? It did not produce an inhibitor.**
10:37:49 **Failure. So taking a learning from one peptide, where**
10:37:54 **conformational constraint gave them a home run, you**
10:37:57 **apply that to bradykinin, destroy all activity. Not**
10:38:02 **applicable.**
10:38:04 **MS. KUZMICH: No further questions on direct,**

10:38:06 Your Honor.

10:38:06 THE COURT: All right. Let's take a stretch.

10:38:08 (Short recess taken.)

10:52:00 THE COURT: All right. Take your seats, please.

10:52:01 Mr. James?

10:52:02 MR. JAMES: Good morning, Your Honor.

10:52:03 THE COURT: Good morning.

10:52:04 MR. JAMES: With your permission, we'll hand up some cross-examination binders.

10:52:08 THE COURT: Yes, indeed.

10:52:13 (Binders handed to the Court and to the witness.)

10:52:17

10:52:21 MR. JAMES: There are two binders.

10:52:23 THE COURT: I see it.

10:52:23 MR. JAMES: Deposition transcripts and report.

10:52:25 THE COURT: Got it.

10:52:46 Doctor, you can move the side here. Move other stuff out of your way.

10:52:49

10:52:50 CROSS-EXAMINATION

10:52:51 BY MR. JAMES:

10:52:52 Q. Good morning, Dr. Walensky.

10:52:53 A. Good morning.

10:52:54 Q. I'd like to talk to you about your opinion on claim construction.

10:52:57

10:53:00 MR. JAMES: Could we put up Claim 14 of the '333

10:53:03 **patent?**

10:53:04 **BY MR. JAMES:**

10:53:05 Q. **You understand that this is the claim in suit?**

10:53:07 A. **Yes.**

10:53:07 Q. **Correct?**

10:53:08 A. **Yes.**

10:53:08 Q. **And Claim 14 is directed to a peptide; right?**

10:53:12 A. **Yes.**

10:53:12 Q. **It's a ten amino acid peptide?**

10:53:15 A. **Yes.**

10:53:15 Q. **And the amino acids are outlined in the claim; is that right?**

10:53:19 A. **Yes.**

10:53:20 Q. **You understand the amino acid sequence of that peptide; is that right?**

10:53:24 A. **Yes.**

10:53:25 Q. **And we can agree that's the sequence of icatibant; is that right?**

10:53:30 A. **If that's what you are telling me. From that, I'm looking at the sequence and I can see what the sequence is.**

10:53:36 Q. **So you don't know whether or not that's the sequence of icatibant?**

10:53:39 A. **Are we talking about me reading that claim to you as it stands or are we interpreting more about trade names of medications?**

10:53:43

10:53:46

10:53:47 Q. **I'm asking you if you know that that is the sequence of icatibant so that you and I can use the word icatibant to talk about that sequence?**

10:53:53 A. **Absolutely. I thought you were asking me a different question.**

10:53:56 Q. **You understand that's the sequence of icatibant?**

10:53:58 A. **Yes. Icatibant is listed in the claim.**

10:54:02 Q. **And then below the sequence of icatibant, the claim talks about physiologically tolerable salt of said peptide; right?**

10:54:10 A. **Yes.**

10:54:10 Q. **And you understand what that means; is that right?**

10:54:13 A. **Yes.**

10:54:14 Q. **There's not any ambiguity in that phrase, is there?**

10:54:19 A. **There isn't.**

10:54:19 Q. **And the claim, Claim 14, does not recite any biological activity whatsoever; right?**

10:54:24 A. **Right.**

10:54:25 Q. **If we can put up demonstrative PDX-3.4. This is a demonstrative that you used on your direct examination; is that right?**

10:54:35 A. **Correct.**

10:54:36 Q. **And you are, as it shows at the bottom of that slide, reading in the phrase "with bradykinin antagonist activity"; right?**

10:54:45

10:54:45 A. **Correct.**

10:54:46 Q. **If we could look at the next demonstrative, PDX-3.5,**
10:54:53 **the bases for you reading in that activity, that language,**
10:55:03 **the bases are laid out on PDX-3.5?**

10:55:07 A. **Correct.**

10:55:07 Q. **So you read into the claim based on the language in**
10:55:10 **the specification, the title, the abstract, and biological**
10:55:15 **data in the '333 patent; is that right?**

10:55:17 A. **When I was asked to look at that claim, my**
10:55:20 **understanding is that one that does that analysis begins**
10:55:22 **with the explicit claim term language and then continues**
10:55:25 **on.**

10:55:26 Q. **But the claim term language unambiguously defines the**
10:55:36 **peptide. Is that correct?**

10:55:38 A. **Correct.**

10:55:40 Q. **Now, let's look at Claim 1 of the '7,803 patent. And**
10:55:54 **Claim 1 of the '7,803 patent lists 13 different positions;**
10:55:58 **right?**

10:55:59 A. **Correct.**

10:55:59 Q. **And for nine of those positions, it only lists a**
10:56:03 **single option; right? That's B, C, E, F, K, Q, M, and F'**
10:56:14 **and I; right?**

10:56:15 A. **Correct.**

10:56:16 Q. **And for A, it lists five positions, five different**
10:56:23 **options. I'm sorry?**

10:56:24 A. **Correct.**

10:56:24 Q. **And for G, there are three different options; is that right? Those are cis-indo, cis-exo and tran-octahydroindole 2-carboxylic acid; right?**

10:56:41 A. **I believe that's correct.**

10:56:41 Q. **So for the sequence A through I, there are five times 3 or 15 peptides outlined; correct?**

10:56:48 A. **I believe so, yes.**

10:56:54 Q. **And then there's a set of options at the Z position; right?**

10:56:58 A. **Correct.**

10:57:02 Q. **And the Z position, there's no ambiguity about the compounds that are identified in the Z group; is that right?**

10:57:10 A. **Correct.**

10:57:10 Q. **And then with respect to the P position, there are seven different options; right?**

10:57:17 A. **Right.**

10:57:18 Q. **And there's no ambiguity there either; right? A person of skill in the art could sit down and write up every single peptide that is delineated in that claim; correct?**

10:57:30 A. **Correct. Over 1100.**

10:57:31 Q. **Now, you are also reading into this claim the activity with bradykinin antagonist activity; right?**

10:57:42 A. **No. I was asked to analyze the claim terms Z and P in**
10:57:46 **the context of Dr. Bachovchin's interpretation of these**
10:57:49 **claim terms, which I disagreed with.**
10:57:51 Q. **Okay.**
10:57:53 A. **That was my analysis, I was asked to look at those**
10:57:56 **claim terms because Dr. Bachovchin in my opinion read into**
10:58:00 **things in terms of language that wasn't there. He read into**
10:58:03 **Z as you know, and he read into P that no linkage, no option**
10:58:10 **is preferred. I was asked to make that analysis.**
10:58:12 Q. **He testified, there's a transcript, but you'll agree**
10:58:14 **that P does allow for a direct linkage; is that correct?**
10:58:18 A. **It does.**
10:58:19 Q. **And that would mean that there would be nothing at the**
10:58:21 **P position; right?**
10:58:22 A. **That's a choice.**
10:58:23 Q. **All right.**
10:58:25 A. **He said it was the preferred choice.**
10:58:27 Q. **Now, am I correct that the claim of the '7,803 patent**
10:58:43 **does not recite any particular biological activity?**
10:58:46 A. **Correct. I was asked to analyze Z and P.**
10:58:51 Q. **Right. But my question is, Doctor: It does not**
10:58:53 **recite any particular biological activity, does it?**
10:58:56 A. **That's correct.**
10:58:57 Q. **So let's look at DDX-5-1.**
10:59:16 **Now, Dr. Walensky, if you take Claim 1 of the**

10:59:21 '7,803 patent and you select the very first option for each
10:59:25 of the 13 groups, the result is Fmoc-icatibant; is that
10:59:32 correct?
10:59:32 A. If you want to -- if you want to agree that we're
10:59:35 calling that sequence icatibant, then I'm happy to call it
10:59:38 that, but I want to make sure that when you call it
10:59:40 icatibant, you mean the final product icatibant, because you
10:59:43 used that in two different ways, and I want to make sure
10:59:46 that we are precise that we're calling icatibant the final
10:59:49 drug.
10:59:49 Q. Well, I will ask the questions. Okay? We agreed
10:59:54 earlier the sequence that was in Claim 14 of the '333 patent
10:59:57 is icatibant; is that right?
10:59:58 A. Right. But I want to be very precise with my answers
11:00:01 because you use icatibant in two different ways, and I want
11:00:04 to make sure we're defining it and I'm agreeing to the
11:00:06 correct way, and I'm just saying that the correct way that I
11:00:09 would use icatibant as the amino acid sequence pictured
11:00:13 there as the final peptide throughout.
11:00:15 THE COURT: Mr. James, why don't you agree on
11:00:17 convention so that the fact-finder doesn't get lost.
11:00:19 MR. JAMES: Okay.
11:00:20 THE COURT: Okay?
11:00:21 BY MR. JAMES:
11:00:22 Q. Dr. Walensky, I think we agreed earlier, I don't think

11:00:25 **I've used this in two different ways, the sequence D-Arg,**
11:00:31 **D-Arginine, arginine, proline, hydroxyproline, glycine,**
11:00:37 **thienylalanine, serine, D-Tic, Oic, arginine is the sequence**
11:00:41 **of icatibant; correct?**
11:00:42 A. **Correct.**
11:00:42 Q. **Correct?**
11:00:43 A. **Correct.**
11:00:43 Q. **And the first entry in the Z group is Fmoc; right? So**
11:00:50 **if one just takes the first entry of each of these groups,**
11:00:58 **one derives Fmoc-icatibant; is that correct?**
11:01:00 A. **We can agree to that nomenclature.**
11:01:03 Q. **Now, let's look at DDX-5-2. DDX-5-2, I have put up**
11:01:25 **the sequence of Claim 14 of the '333 patent and juxtaposed**
11:01:32 **it with the sequence of Claim 1 of the '7,803 patent.**
11:01:36 **Do you see that?**
11:01:37 A. **I do.**
11:01:37 Q. **And you understand that what we're talking about in**
11:01:45 **this case is whether the sequence of Claim 14 of the '333**
11:01:50 **patent is an obvious variant of this sequence of Claim 1 of**
11:01:55 **the '7,803 patent; is that correct?**
11:01:57 A. **Correct.**
11:01:58 Q. **Now, the only -- well, let me withdraw that.**
11:02:04 **The amino acid sequence of these two claims is**
11:02:09 **identical; right?**
11:02:11 A. **Correct.**

11:02:11 Q. **The amino --**

11:02:14 A. **As long as you are representing very clearly that --**
11:02:18 **this is important. As long as you are representing very**
11:02:20 **clearly that those circles, which are a two-dimensional**
11:02:25 **schematic, are the final product where those circles don't**
11:02:27 **have protection or any other entities that are not being**
11:02:31 **listed there.**

11:02:31 **We can agree that those representations**
11:02:34 **could be made a schematic, that that is the final purified**
11:02:38 **product with no protection groups on the top and the same**
11:02:42 **holds for the bottom. If we can discuss that specific clear**
11:02:46 **scientifically precise definition, then, yes, I'm happy to**
11:02:49 **go along with that.**

11:02:50 Q. **Well, it's your position that it's directed to a final**
11:02:54 **product in Claim 1 of the '7,803 patent. Correct?**

11:02:59 A. **Let's call it composition then.**

11:03:01 Q. **But I think we can agree that whatever these different**
11:03:05 **amino acids mean they have the same meaning in Claim 14 of**
11:03:10 **the '333 patent as they do in Claim 1 of the '7,803 patent;**
11:03:14 **is that right?**

11:03:14 A. **Correct. Can I explain why I think it's important?**

11:03:18 **THE COURT: So, Doctor --**

11:03:20 **MR. JAMES: Sorry, Your Honor.**

11:03:20 **THE COURT: Their rules, just like in your case.**
11:03:25 **He gets to ask the questions. If I think things are getting**

11:03:29 **out of whack, I will -- try your best to answer.**

11:03:34 **THE WITNESS: I will try to fit into my answer.**

11:03:36 **THE COURT: If you can't respond precisely, you need to tell us.**

11:03:40 **THE WITNESS: It's kind of why I'm making this point earlier.**

11:03:42 **THE COURT: All right.**

11:03:44 **MR. JAMES: Thank you, Your Honor.**

11:03:45 **BY MR. JAMES:**

11:03:46 Q. **So you would agree with me that to the extent that there are no side chain protecting groups identified in the '333 patent claim sequence, there are likewise no such side chain protecting groups identified in Claim 1 of the '7,803 patent; right?**

11:04:05 A. **Now we're talking. Yes.**

11:04:07 Q. **Both sequences have D-Tic at the seven position; right?**

11:04:17 A. **Yes.**

11:04:18 Q. **You spent a lot of time talking about that in your testimony earlier; is that right?**

11:04:21 A. **I did.**

11:04:22 Q. **And both sequences have Oic at the eight position; right?**

11:04:26 A. **Correct.**

11:04:27 Q. **So, and you offered the opinion that that sequence**

11:04:36 would be understood to be from the claims in the context of
11:04:40 these claims bradykinin antagonists; right?
11:04:43 A. Correct.
11:04:43 Q. So they're both pointed at the same lock; right?
11:04:48 A. I was asked to talk about Z and P, but I understand
11:04:52 your question.
11:04:53 Q. Can you answer it? They're both pointed at the same
11:04:56 lock, aren't they?
11:04:57 A. I was asked to explain the compositions and what the
11:05:00 meaning of Z and P is. And if you read beyond the claim,
11:05:03 then, yes.
11:05:05 Q. The information in the -- well, let me withdraw that.
11:05:13 The only difference between the obviousness-type
11:05:17 double patenting reference claim, the '7,803 patent, Claim
11:05:23 1, and Claim 14 of the '333 patent, the only difference is
11:05:27 Fmoc; right?
11:05:28 A. In that example.
11:05:29 Q. And you spent some time --
11:05:44 THE COURT: Mr. James, is this example directly
11:05:47 from the patent claims, the one that we're looking at?
11:05:49 MR. JAMES: Yes, Your Honor. If we could back
11:05:52 up one to DDX-5-1, Mr. Chase.
11:05:59 So, Your Honor, the witness and I agreed that if
11:06:02 you take from the '7,803 claims, if you take the very
11:06:06 first option, this is exactly the sequence you get there,

11:06:09 and from the '333 patent claim, that you have the same
11:06:12 sequence.
11:06:13 THE COURT: Okay.
11:06:13 BY MR. JAMES:
11:06:17 Q. You spent some time in your testimony talking about
11:06:19 how nobody of skill in the art would have selected at the
11:06:23 seven position a conformationally contained amino acid like
11:06:29 D-Tic based on what was known at the time; right?
11:06:31 A. Correct.
11:06:46 Q. But in our case here, D-Tic has already been selected
11:06:49 in that claim, hasn't it?
11:06:51 A. It depends what time and what knowledge you are
11:06:53 allowed to know about when you are making the answer to that
11:06:56 question.
11:06:56 Q. The comparison that we are making here in this
11:07:00 obviousness-type double patenting case is between these
11:07:03 claims, and the selection of D-Tic at Position 7 has already
11:07:08 been made there. Right?
11:07:09 A. No. My understanding of my decision and opinion based
11:07:13 upon the analysis is that I am supposed to take the explicit
11:07:17 claim language from '7,803, put it into the prior art, and
11:07:21 then answer the question, is the claim language in Claim 14
11:07:26 of the '333 patent invalid based upon the '7,803 language in
11:07:31 the context of the prior art.
11:07:34 That's what I was asked to render an opinion on.

11:07:37 Q. **So you were looking at whether or not D-Tic and Oic, the use of D-Tic and Oic, would have been obvious over the prior art. Right?**

11:07:45 A. **No. Taking the claim language from '7,803 and putting that in the context of the prior art, that is what I was asked to do. It is about what information you are allowed to use to analyze, to answer the question that you are asking me.**

11:08:01 **That has to be defined.**

11:08:02 Q. **The information that we have in front of us, comparing these two claims, is that we start with D-Tic at the 7 position and Oic at the 8 position. Right?**

11:08:13 A. **Yes.**

11:08:13 Q. **And those are both conformationally constrained amino acids. Right?**

11:08:18 A. **Yes.**

11:08:18 Q. **And they are exactly the same amino acids in Claim 14 of the '333 patent. Right?**

11:08:26 A. **Yes. But you are asking me to compare them on a slide but you are not --**

11:08:29 Q. **I am just asking you whether you agree or not that it's the very same amino acids at the 7 and 8 position of those two claims.**

11:08:39 A. **What's on the slide is the same. We all agree to that. I am pointing out the analysis question, I am not a**

11:08:44 **lawyer, but the analysis question is actually a different**
11:08:47 **question than what you are asking.**
11:08:49 **THE COURT: I think what you should anticipate**
11:08:50 **is that counsel for plaintiff will ask some followup**
11:08:55 **questions. So you don't need to be concerned.**
11:08:58 **THE WITNESS: Okay.**
11:09:00 **MR. JAMES: Thank you, Your Honor.**
11:09:01 **BY MR. JAMES:**
11:09:02 Q. **So looking at this difference between these two**
11:09:05 **claims, I think we agreed a moment ago that the only**
11:09:08 **difference between these two claims is the presence of this**
11:09:11 **Fmoc. And in January of 1989, a person of ordinary skill in**
11:09:20 **the art would have known how to remove an Fmoc from the**
11:09:24 **N-terminus of Fmoc icatibant?**
11:09:30 A. **During the construction of a peptide, yes, with that**
11:09:33 **qualification.**
11:09:33 Q. **I believe what you said was we shouldn't be fooled,**
11:09:38 **that Fmoc can do two things.**
11:09:41 A. **Correct.**
11:09:41 Q. **Fmoc can be put on and taken off and put on and taken**
11:09:46 **off during construction of a peptide?**
11:09:48 A. **Correct.**
11:09:48 Q. **But it can also be left on at the end. Right?**
11:09:51 A. **On purpose.**
11:09:52 Q. **But it is the very same Fmoc. Right?**

11:09:54 A. **Correct.**

11:09:54 Q. **You could take it off, just like you could take it off every other time during the synthesis of the peptide if you wanted to. Right?**

11:10:01 A. **You are oversimplifying and conflating the two roles.**

11:10:04 Q. **My question is, you could do it if you wanted to. Right?**

11:10:08 A. **In a particular context. I must be precise.**

11:10:20 Q. **It's true, is it not, that in a typical Fmoc synthesis process, the Fmoc -- the Fmoc amino acids are put on one at a time and every single time the Fmoc is taken off as you build up that peptide chain. Right?**

11:10:38 A. **Not every time, because at the last time it was not. Again, we can't oversimplify. During peptide synthesis, you are absolutely correct, on-off, on-off, during the construction of peptides. We don't disagree there.**

11:10:53 Q. **And the portion of taking the Fmoc off of the amino acid is carried out by exposure to a weak base that we call piperidine. Right?**

11:11:06 A. **Correct.**

11:11:06 Q. **If you exposed Fmoc-icatibant, like we have put up here from Claim 1 of the '7,803 patent, to the weak base piperidine, that Fmoc would come right off, wouldn't it?**

11:11:20 A. **Tricky question, but that is not a reaction that is done. In the context -- this goes back, Your Honor, to my**

11:11:27 **clarification about peptides being, agreeing that peptide is**
11:11:31 **the final product with no protecting groups. You are trying**
11:11:34 **to apply a chemical reaction that is done during peptide**
11:11:37 **synthesis to a peptide that is a final product.**
11:11:40 **The answer to that more precise question would**
11:11:42 **be no.**
11:11:43 Q. **Dr. Walensky, I think what you are saying is that, if**
11:11:49 **you wanted to, you could leave the Fmoc on and it might have**
11:11:52 **some effect. Right?**
11:11:54 A. **The literature says that it does, yes.**
11:11:55 Q. **But if you wanted to take it off, is it not true that**
11:11:59 **you could also do that?**
11:12:00 A. **Not from that, what you picture on the slide.**
11:12:02 Q. **You are saying you could not take the Fmoc off. If**
11:12:06 **you exposed it to piperidine, the Fmoc would come off,**
11:12:08 **wouldn't it?**
11:12:10 A. **No. I am saying that a POSA, before January of 1989,**
11:12:14 **considering the question of would you remove Fmoc from that**
11:12:17 **peptide in its current form, the answer is no.**
11:12:20 Q. **I understand it is your position that a POSA would not**
11:12:24 **take it off. My question is a little different. My**
11:12:26 **question is, if a person of skill in the art decided that**
11:12:30 **they wanted to take it off, they would have known how.**
11:12:33 **Right?**
11:12:34 A. **Before the peptide was finished. And we can keep**

11:12:36 doing this. But my opinion is going to be the same. It
11:12:40 would be taken off before the peptide is finished. That's
11:12:42 what the literature says. You know what? It hasn't
11:12:44 changed.
11:12:45 THE COURT: After the peptide is finished could
11:12:47 a POSA, in the physical world, remove the Fmoc?
11:12:49 THE WITNESS: It is not done in automated solid
11:12:54 phase peptide systems.
11:12:55 THE COURT: Understood. I think Mr. James was
11:12:56 trying to get at another point. In the physical world would
11:12:59 a POSA be able to do that?
11:13:00 THE WITNESS: That is a great question. In the
11:13:02 physical world, if you hand me that peptide right now and I
11:13:06 threw in base, the Fmoc would probably fall off. No one
11:13:09 would ever do that, there is actually a reason no one would
11:13:12 do it.
11:13:13 I haven't seen an example, maybe you will show
11:13:15 me one, but I haven't seen an example in any of the material
11:13:18 that I have reviewed in this case nor any of the material
11:13:21 that I have reviewed ever since becoming a peptide chemist
11:13:23 that that reaction would be done that way.
11:13:26 Let me answer why. I think it's a very
11:13:28 important point.
11:13:29 THE COURT: Well, I don't want to hijack Mr.
11:13:33 James's examination.

11:13:34 **THE WITNESS: Just to finish my answer --**

11:13:37 **THE COURT: Doctor, let Mr. James pick up at this point.**

11:13:40 **BY MR. JAMES:**

11:13:41 Q. **So we are all on the same page, Dr. Walensky, if you have Fmoc-icatibant, regardless of the context, if you exposed it to a weak base, the Fmoc would come off. Correct?**

11:13:56 A. **You and I are not going to agree on the answer to that question. So I can tell you that you can create chemistry for a nonrealistic world, what is done and not done. We can talk in the realm of fantasy. And I am happy to answer your question in the realm of fantasy.**

11:14:09 **I thought I was here to answer your question in the realm of reality. The answer in the realm of reality is no. In the realm of fantasy, could that possibly ever happen if you just threw base into a final product? That could happen, and a whole lot of other things, which is why it is not done.**

11:14:25 Q. **Let's just go back to Claim 1 of the '7,803 patent for a moment, Mr. Chase.**

11:14:41 **Now, I am correct that the words final product don't appear anywhere in that claim, do they?**

11:14:50 A. **That's correct. The patent is claiming a peptide of that specific and unequivocally clear composition.**

11:14:54

11:14:57

11:14:59

11:15:03 Q. **Can we look at Breipohl, that is DTX-60, at Page 4. I**
11:15:11 **believe this is a reference you have looked at in the course**
11:15:14 **of your studies in this case. Right?**
11:15:16 A. **Let me see here.**
11:15:27 **Yes.**
11:15:27 Q. **And I recognize that it's a different peptide. But at**
11:15:41 **the top of this page, there is a reaction arrow. Correct?**
11:15:46 A. **Are we on Page 19?**
11:15:48 Q. **Yes. Page 19, I believe Page 4 of the exhibit, there**
11:15:52 **is a reaction arrow there. Right?**
11:15:53 A. **Yes.**
11:15:54 Q. **And it's talking about adding Fmoc protected amino**
11:16:00 **acids to the chain. Right?**
11:16:02 A. **Yes.**
11:16:02 Q. **And it says there are 23 cycles there. Right?**
11:16:07 A. **Yes.**
11:16:07 Q. **And in those 23 cycles, 20 percent piperidine is**
11:16:15 **added. Right?**
11:16:15 A. **Correct.**
11:16:15 Q. **So in the real world, in every single one of those 23**
11:16:19 **cycles, that piperidine knocked that Fmoc right off the end**
11:16:23 **of the peptide, didn't it?**
11:16:26 A. **We agree perfectly on that. Peptide under**
11:16:29 **construction.**
11:16:29 Q. **So let's look at the '7,803 patent specification.**

11:16:39 **Mr. Chase, if we could put up Column 1.**

11:16:44 **At the top of Column 1, Dr. Walensky -- you have read the specification of the '7,803 patent. Right?**

11:16:55 A. **I have.**

11:16:55 Q. **You see in the third paragraph from Lines 9 to 11 there is a reference right about Line 10, European Patent Application No. 370,453. Do you see that?**

11:17:10 A. **I do.**

11:17:10 Q. **You recognize that as the European equivalent of the '333 patent. Right?**

11:17:15 A. **If you tell me that's what it is.**

11:17:16 Q. **So you don't know whether or not that is what it is?**

11:17:19 A. **I don't know all the numbers, no.**

11:17:20 Q. **You would agree with me, though, that the inventors of the '7,803 patent, they started out with, one of the compounds they started out with was icatibant. Right?**

11:17:31 A. **I don't know that.**

11:17:32 Q. **Let's look at Example 1, Mr. Chase.**

11:17:57 **I will help you. It's in your binder there, Dr. Walensky, if you want to look at it, I can direct you to it while we are finding it on the screen.**

11:18:24 **It's in Column 18, it begins at Line, I think that's 43. And in this example, it talks about the assembly of Fmoc-D-Arginine-Arginine-Proline-hydroxyproline-glycine-thienylalanine-serine-D-Tic-Oic-Arginine-Hydroxyl. Right?**

11:18:55 A. **Column 18?**

11:18:56 Q. **Column 18.**

11:18:57 A. **Got it.**

11:19:25 **(Pause.)**

11:19:33 Q. **Are you there?**

11:19:34 A. **Yes.**

11:19:35 Q. **That is Fmoc-icatibant. Correct?**

11:19:41 A. **It appears to be.**

11:19:41 Q. **If we look at Column 10, Lines 31 to 33 --**

11:19:56 A. **We are going back to Column 10?**

11:19:58 Q. **Yes.**

11:20:00 A. **Yes.**

11:20:00 Q. **There it talks about urethane -- we are at about Line 31 -- urethane protective groups such as, for example, what they refer to as Boc or Fmoc are used as temporary amino protective groups. Right?**

11:20:20 A. **Correct.**

11:20:21 Q. **There they are talking about during the peptide synthesis. Correct?**

11:20:25 A. **Correct.**

11:20:25 Q. **And if you look at Column 12, Mr. Chase, if you could pull up Column 12, Line 65, to Column 13, Line 1 --**

11:20:40 A. **What?**

11:20:41 Q. **Column 12. We will pull it up on the screen for you. Column 12, Line 65 to Column 13, Line 1, there they are**

11:20:46

11:20:51 talking about when they use the Fmoc protective group with
11:20:59 their Model 430A automatic peptide synchronizer. Right?
11:21:04 A. Yes, I have used that very one.
11:21:06 Q. And that is a machine where you put in a sequence that
11:21:13 you want and it spits it out for you. Right?
11:21:17 A. It's a little more complicated than that. But, sure.
11:21:21 Q. Then if we look at Column 13, Lines 13 to 15 -- one
11:21:32 more thing here, you will see that Column 13, you will see
11:21:46 it says that the Fmoc protective group was eliminated with a
11:21:50 20 percent strength solution of piperidine in DMF in the
11:21:54 reaction vessel. Right?
11:21:56 A. Correct.
11:21:56 Q. So what this is teaching is that the Fmoc method could
11:22:04 be used with the automated synchronizer to make
11:22:08 Fmoc-icatibant. Right?
11:22:10 A. Yes.
11:22:10 Q. And a person of skill, if they wanted to take off the
11:22:14 Fmoc, they could program the machine to do that at the end
11:22:17 of the synthesis as well. Correct?
11:22:19 A. That is correct, on the resin during the synthesis, if
11:22:22 that was the decision, to make it without it, absolutely.
11:22:24 Q. So really, the only difference between those two
11:22:28 things would be punching the buttons in the machine. Right
11:22:32 ?
11:22:33 A. The only difference between those things is deciding

what you want to make. It's not about punching the buttons. You punch the buttons to do what you want. The only decision is the scientist's decision to decide what they want to make.

That's what you punch in the buttons. If I want to make a peptide that leaves the Fmoc on, then I program it that way. If I want to make a peptide that has it off, then I program it a different way.

It's a computer program, a computer that's attached to a machine.

Q. So going back to what we were talking about earlier, if one decided one wanted to make icatibant from Fmoc-icatibant, one could do so?

A. On the resin, yes.

Q. You could do it off the resin as well, couldn't you?

A. This is doing it on the resin. So I am trying to answer your question accurately.

Q. I understand you want to stay -- you want to keep your answer tied to that resin. But I am asking you a different question. Whether it was on the resin or off the resin --

A. Now you are asking --

Q. If you decided you wanted to take Fmoc off of Fmoc-icatibant to make icatibant, you could do so. Right?

A. No. I am sorry. I need to answer the question precisely.

11:23:48 **THE COURT: Do your best, Doctor.**

11:23:50 **THE WITNESS: Even though there is a desire for**
11:23:52 **me to be general and not precise. And I am kind of a**
11:23:56 **precise guy.**

11:23:57 **He is asking me two questions. Am I allowed to**
11:24:00 **answer the two questions?**

11:24:01 **THE COURT: I think it's one question.**

11:24:03 **BY MR. JAMES:**

11:24:03 Q. **It's one question.**

11:24:04 A. **It's one question if you gloss over the fact that it's**
11:24:07 **two, that's the problem. The answer to your first question**
11:24:10 **is if you wanted to take the Fmoc off on the machine, if**
11:24:14 **that was your desire, you would do so.**

11:24:16 **If you wanted to take the Fmoc off, off the**
11:24:19 **machine, there is another way to do that that doesn't**
11:24:21 **involve programming the machine. And if you would like me**
11:24:23 **to explain how that works, that's a different answer to the**
11:24:26 **same question, that is also chemically possible. But it's**
11:24:30 **still not the answer that he wants me to say. But I am**
11:24:33 **happy to explain it.**

11:24:35 Q. **I think that we are on the same page, if you intended**
11:24:39 **to make icatibant from Fmoc-icatibant, whether you had the**
11:24:43 **Fmoc-icatibant on the resin or not on the resin, you could**
11:24:46 **do so. Correct?**

11:24:47 A. **As long as you continue to work on the peptide with**

11:24:51 the resin. You would have to do that with the resin to take
11:24:56 the Fmoc off if you wanted to not use the machine. You can
11:25:00 definitely do that. But you would still be taking the resin
11:25:03 off the machine and decide to do it manually.
11:25:05 The only reason that I want to be precise here,
11:25:08 besides the fact that it is important, is that I have done
11:25:11 it every way that you could imagine and so I want to be
11:25:14 precise on how you would do it and not to oversimplify so
11:25:17 that the wrong impression is given.
11:25:27 THE COURT: I think essentially he has agreed
11:25:30 with you.
11:25:31 THE WITNESS: What I have agreed with is you can
11:25:32 take the Fmoc group off, non-automatically, but still with
11:25:39 the resin --
11:25:40 THE COURT: I think what I understand, Doctor,
11:25:41 is that wouldn't be your preference.
11:25:43 THE WITNESS: I don't think it would be anyone's
11:25:45 preference.
11:25:45 THE COURT: Or any POSA's preference.
11:25:47 THE WITNESS: But I would like to make it clear
11:25:49 that if you want to do it old school, you could do it
11:25:53 non-automated old school. But it is still on the resin or
11:25:57 even off the resin with protective groups.
11:25:59 That first example he pointed to was an example
11:26:01 of that. But he stopped short of going to the end of that

11:26:05 **reaction in that first article that he took me to. We went**
11:26:08 **through the first half of the reaction scheme. But he**
11:26:10 **stopped. If we went through the rest of the reaction**
11:26:14 **scheme, we could talk about what he is asking.**
11:26:17 **BY MR. JAMES:**
11:26:17 Q. **Dr. Walensky, as part of your work on this case, you**
11:26:20 **relied on an expert report by Dr. Jacobsen. Correct?**
11:26:25 A. **Correct.**
11:26:26 Q. **Did you ever look at Dr. Jacobsen's deposition**
11:26:29 **transcript in this case?**
11:26:30 A. **I don't think I did.**
11:26:31 Q. **I would like to show you a very short excerpt from**
11:26:35 **that.**
11:26:36 **MR. JAMES: I would like to hand it up, with the**
11:26:38 **Court's permission.**
11:26:39 **THE COURT: To him, yes. You are going to show**
11:26:42 **it on the screen.**
11:26:46 **MR. JAMES: Yes.**
11:26:51 **THE WITNESS: I wouldn't say I relied on it, but**
11:26:53 **I am aware of it. I relied on my own opinions.**
11:26:57 **BY MR. JAMES:**
11:26:58 Q. **You cited to his expert report in your expert report?**
11:27:04 A. **Yes. I am aware of him being a chemist and that he**
11:27:06 **provided information. I am a peptide chemist.**
11:27:09 Q. **Let's put up a very short excerpt from his deposition**

11:27:13 **transcript. I will give you the citation.**

11:27:19 **Mr. Chase, if you could put up -- I will direct**

11:27:32 **you, Dr. Walensky.**

11:27:54 **MR. JAMES: My apologies, Your Honor. I just**

11:27:56 **didn't write down that page number in my outline.**

11:28:00 **(Pause.)**

11:28:05 **BY MR. JAMES:**

11:28:06 Q. **All right. Dr. Walensky, it's Page 198, and beginning**

11:28:11 **at line 13, and then running down to line 3 of Page 199.**

11:28:20 **And Dr. Jacobsen there said, he's asked:**

11:28:25 **"So going back to Paragraph 60 of your report --**

11:28:27 **"Answer: Yes.**

11:28:30 **"Question: -- and that structure that you have**

11:28:31 **listed at the top there, Fmoc, D-Arginine, arginine,**

11:28:36 **proline, hydroxyproline, glycine, thienylalanine, serine,**

11:28:41 **D-Tic, Oic, arginine hydroxyl, that was one of the**

11:28:46 **structures that was in Claim 1 of the '7,803 patent,**

11:28:50 **correct?**

11:28:51 **"Answer: Correct."**

11:28:51 **Right? And so just so we're on the same page,**

11:28:56 **Dr. Walensky, there's no resin attached in that, to that**

11:29:00 **hydroxyl N in that question; right?**

11:29:02 A. **Well, I don't know how you asked him the question. I**

11:29:05 **mean, what his understanding of your question was.**

11:29:07 Q. **There's no resin mentioned in that testimony, is**

11:29:10 there?

11:29:10 A. You didn't mention it. You gave a composition.

11:29:15 Q. And then it says, as of 1989, a person of ordinary skill in the art could remove the Fmoc from that structure to obtain icatibant; correct? And the answer was, yeah, they would be familiar with the methodology to do that.

11:29:27 A. If that --

11:29:28 Q. You would agree with that; is that correct?

11:29:29 A. Only if that was the plan to do that from the purposes of constructing that peptide. You're reading into that, I believe, that, you know, you could go from A arrow to B. That's not my read of what he's saying. He's saying if you wanted to make that peptide without the Fmoc, would a POSA know how to do that? Sure. They would program in the computer, the computer synthesizer differently. I think you are reading into that the question of can you chemically go from A to B with that exact structure in a reaction vessel. That's a little bit more than what you are asking. You're generally asking him, can you make a peptide with or without Fmoc? Sure.

11:30:03 Q. Thank you.

11:30:08 I'd like to now turn to demonstrative 3.7 that you put up on the screen earlier. And you said that, you're talking about the Z group in this slide. Is that correct?

11:30:19 A. Yes.

11:30:19 Q. **And you said that the common chemical feature of all**
11:30:23 **the Z groups indicates permanence?**
11:30:26 A. **Right.**
11:30:26 Q. **We look at the next demonstrative, which is 3.8. And**
11:30:32 **I believe that you pointed out that although all of the**
11:30:38 **other groups are acyl groups, in fact, the Fmoc is a**
11:30:47 **urethane; is that correct?**
11:30:48 A. **Correct.**
11:30:48 Q. **Now, you talked about some reason why the prior art**
11:31:04 **would have suggested leaving on the Z group; right?**
11:31:07 A. **Correct.**
11:31:07 Q. **Now, there were prior art bradykinin antagonists in**
11:31:15 **the literature; is that correct?**
11:31:17 A. **Correct.**
11:31:17 Q. **And one of those, I think you're familiar with, is**
11:31:21 **B-3824?**
11:31:22 A. **Correct.**
11:31:22 Q. **So if we could look at DDX-2-77, just so we have**
11:31:30 **something to facilitate the discussion, Doctor. We have**
11:31:37 **B-3824 from the '993 patent, Example 20, the sequence**
11:31:42 **there at the bottom compared to Claim 1 of the '7,803**
11:31:48 **patent.**
11:31:49 **Do you see that?**
11:31:49 A. **I do.**
11:31:50 Q. **Okay. And Claim 1 of the '7,803 patent, we've said**

11:31:56 **that the N protecting genus is at the Z group, and that's**
11:31:59 **all the groups that you talked about in your testimony;**
11:32:01 **right?**
11:32:01 A. **Correct.**
11:32:02 Q. **And then the P group; right?**
11:32:04 A. **Correct.**
11:32:04 Q. **Now, B-3824 is an example of a prior art bradykinin**
11:32:08 **antagonist that was potent; right?**
11:32:12 A. **Correct.**
11:32:12 Q. **And it has a D-arginine at the zero position?**
11:32:17 A. **Correct.**
11:32:18 Q. **And Claim 1 of the '7,803 patent, one of the options**
11:32:22 **you have there is D-arginine at the zero position?**
11:32:24 A. **Correct.**
11:32:25 Q. **And, in fact, all the rest is identical except for**
11:32:30 **the difference between the DPhe and the D-Tic, and the Thi**
11:32:37 **and the Oic?**
11:32:37 A. **Yes.**
11:32:37 Q. **You would agree with me that B-3824 is an example of a**
11:32:42 **bradykinin antagonist in the prior art that didn't have a Z**
11:32:45 **or a P group?**
11:32:46 A. **Correct. I mean, the bradykinin peptide doesn't have**
11:32:52 **a Z or a P group either, but it's what God made for our**
11:32:55 **bodies.**
11:32:56 Q. **Well, if we look at the '963 patent, you talked about**

11:32:59 **the '963 patent in your direct testimony; correct?**

11:33:02 A. **I did.**

11:33:03 Q. **And if we could, Mr. Chase, if you could put up Column 4 at the top. Well, before we look at that top, if we could look at the bottom of Column 3.**

11:33:16 **I believe, Dr. Walensky, you talked about the table at the bottom of Column 3; right?**

11:33:17 A. **I did.**

11:33:19 Q. **And the N that you are pointing out there, that's the zero position; right?**

11:33:22 A. **So that's --**

11:33:22 Q. **It's on your screen as well?**

11:33:27 A. **That's the position that they are calling before the first amino acid, yes. I mean, people use zero minus one minus two in different ways. Zero pretty much means if you want to be very general, whatever comes before your amino acid sequence.**

11:33:29 Q. **Well, in this particular case, they are identifying N at the zero position; right? It says N-0. Correct?**

11:33:36 A. **Yes. I'm just pointing out that we --**

11:33:37 Q. **In fact, I will ask some questions, and you'll get a chance on redirect to say what you want to say, Doctor.**

11:33:39 **And then if you look at A through, A1 through A9, those are the nine positions that correspond to the**

11:33:44

11:33:48

11:33:50

11:33:51

11:33:55

11:34:01

11:34:03

11:34:06

11:34:09

11:34:09

11:34:15

11:34:17 **sequence of bradykinin; right?**

11:34:19 A. **Okay.**

11:34:20 Q. **That's correct, isn't it?**

11:34:23 A. **What are -- you are not showing me any residue. Is A1 the arginine or is A1 the arginine?**

11:34:27

11:34:29 Q. **I believe A1 is the arginine.**

11:34:33 A. **The arginine or the D-arginine?**

11:34:35 Q. **The arginine?**

11:34:36 A. **The arginine of a natural sequence?**

11:34:38 Q. **Yes.**

11:34:38 A. **Okay.**

11:34:39 Q. **And if you, you can feel free to look at the patent to correct me if I'm wrong. A1 is the arginine?**

11:34:44

11:34:46 A. **Okay. I want to be sure. Hold on.**

11:34:49 Q. **You can look right there in Column 4, in the second paragraph, it talks about A1; right?**

11:34:52

11:34:55 A. **Yes. So that's the natural beginning arginine without the D-Arg in front. Okay. Got you.**

11:35:00

11:35:03 Q. **So I think we're on the same page now that N is the zero position.**

11:35:07

11:35:08 A. **Yes.**

11:35:08 Q. **Right?**

11:35:09 A. **Yes.**

11:35:10 Q. **And in what we just looked at earlier, that was where the D-arginine was in B-3824; right?**

11:35:13

11:35:16 A. **Yes.**

11:35:16 Q. **Okay. Now, let's look at what it says about the N. It says at the top of Column 4 that the N can be a D- or L-amino acid such as D-Arg, D-lysine, or L-thienylalanine, an N-terminal enzyme protecting group selected from the group consisting of, comprising acyl-type protecting groups, aromatic urethane-type protecting groups, alkyl-type protecting groups, or alternately, N is a di- or polypeptide containing amino acids of the D or L configuration, such as Lys-Lys, Met-Lys or Gly-Arg-Met-Lys; right?**

11:36:01 A. **Yes.**

11:36:01 Q. **Now, it doesn't say it can be D-arginine and an acyl protecting group; correct?**

11:36:06 A. **Actually, not really, because, can I explain why I say no to that?**

11:36:11 Q. **The grammar of the sentence is that it's an or, it's an alternate; is that correct?**

11:36:15 A. **Let me just point out - --**

11:36:17 Q. **Am I correct?**

11:36:18 A. **It's all or.**

11:36:20 Q. **It's all or. Yes?**

11:36:21 A. **At the end of the last or, it listed a whole bunch of choices which are more than one thing. I need to answer your question in an honest, truthful, precise way. You are trying to say there's only one thing out there and my answer**

11:36:35 to that is no. And even if there are ors, if you look at
11:36:39 what the ors are, you look at the last or. Gly-Arg-Met-Lys.
11:36:45 How many amino acids is that? Four. Can you have more than
11:36:50 one thing? My answer is yes.
11:36:51 Q. My question wasn't, Doctor, whether or not there could
11:36:53 be more than one thing there. My question was: It doesn't
11:36:53 disclose D-Arg and an acyl-type protecting group; is that
11:36:58 correct?
11:36:58 A. Correct, but it implies that you could have more.
11:37:02 Q. It doesn't suggest D-arginine and a urethane-type
11:37:05 protecting group; right?
11:37:06 A. In this example, it doesn't, but this is not the only
11:37:10 option here.
11:37:14 Q. If we look at Table 4, Column 16, I think you drew the
11:37:18 Court's attention to that. These are examples of bradykinin
11:37:26 antagonists that were tested in the patent; right?
11:37:29 A. Correct.
11:37:30 Q. And you can look at Table 4 and you can look at
11:37:33 Table 5, and can you just confirm for me that there's not a
11:37:36 single example there where there is an acyl protecting group
11:37:41 on the N-terminus of a D-agonism?
11:37:44 A. Not in this particular patent, but there are
11:37:46 definitely in others and also other literature before
11:37:49 1989.
11:37:50 Q. Now, you pointed the Judge to some examples in Table

11:38:01 **5; is that correct?**

11:38:02 A. **Correct.**

11:38:02 Q. **And in particular, Mr. Chase, if you could in Table 5 bring out Examples 55, 56 and 57. Let's expand those, please.**

11:38:22 **And these are three examples you brought to the Court's attention; right?**

11:38:24 A. **I believe I was talking about two of them.**

11:38:26 Q. **Well, I wrote it down. You talked about 55, 56 and 57?**

11:38:32 A. **No.**

11:38:37 Q. **Sorry. I don't have a transcript.**

11:38:37 A. **No, I didn't. I talked about 51 and 52 and I compared 55 and 56.**

11:38:38 Q. **Okay. Well, you compared 55 and 56. Yes.**

11:38:39 A. **But that's the comparison.**

11:38:43 Q. **Right. Okay. Right. So you did not talk about 57; right?**

11:38:45 A. **No, but I'm happy to if you would like.**

11:38:49 Q. **Okay. So let's look at 55. That's the sequence. That's a BK antagonist that does not have an N-terminal acyl or D-arginine; right?**

11:38:50 A. **Correct.**

11:38:56 Q. **And it shows, just to shortcut things here, a little bit of arginine; right?**

11:38:56

11:38:58

11:39:01

11:39:07

11:39:09

11:39:09

11:39:15

11:39:17 A. **Correct.**

11:39:18 Q. **That's what those positive numbers mean over there in the first two columns. And it's also broken down; is that right?**

11:39:25 A. **Correct.**

11:39:25 Q. **That's what the 61 percent means?**

11:39:27 A. **Yes.**

11:39:28 Q. **And then 56 is that very same sequence with the acyl group on it?**

11:39:33 A. **Right.**

11:39:34 Q. **And you get antagonism; right?**

11:39:35 A. **Correct.**

11:39:37 Q. **That's what IB means?**

11:39:37 A. **Yes.**

11:39:39 Q. **Right? And then in 57, you have D-arginine at the N-terminus of that same sequence; right?**

11:39:40 A. **Yes.**

11:39:46 Q. **And it accomplishes antagonism as well; right?**

11:39:48 A. **Correct.**

11:39:49 Q. **So it has the same effect according to this table that putting on the acyl group did?**

11:39:52 A. **In that one example, yes. Now, when you say the same effect, there's no way to know how different they are. There's no data there.**

11:39:53 Q. **The data -- well, all the data we have are that**

11:39:57

11:39:59

11:40:05

11:40:10

11:40:11

11:40:14 **they're both antagonists; right?**

11:40:15 A. **Right.**

11:40:16 Q. **And either they didn't test it or it wasn't broken**
11:40:18 **down at all; right?**

11:40:19 A. **You got it.**

11:40:20 Q. **So let's look at Barabe. I think that you brought**
11:40:25 **Barabe to the Court's attention as well. Right?**

11:40:30 A. **Yes, I did.**

11:40:31 Q. **Okay. It's the very last page of Barabe, the very**
11:40:41 **last paragraph?**

11:40:41 A. **Do you have that in your book or should I go back to**
11:40:44 **mine?**

11:40:44 Q. **I have it in my book. It's JTX-39. Oh, I don't. I'm**
11:40:48 **sorry. I don't.**

11:40:49 A. **Okay.**

11:40:50 Q. **It's in your binder.**

11:40:51 A. **I've got it. I'm with you.**

11:41:03 Q. **Okay. And we talked a little bit about this. I just**
11:41:10 **want to make sure we're on the same page. That there was**
11:41:13 **some sign of histamine release by these bradykinin**
11:41:16 **antagonists; right?**

11:41:18 A. **Yes.**

11:41:18 Q. **And so they acetylated the N-terminal amide; is that**
11:41:24 **right?**

11:41:24 A. **Yes.**

11:41:24 Q. **That means they, to put it in parlance we've been**
11:41:28 **using, they added the acyl group to the N-terminus of**
11:41:32 **the peptide; right? And here it was an acetyl group;**
11:41:36 **right?**
11:41:36 A. **Yes.**
11:41:36 Q. **Okay. And acetyl group, that's not one of the groups**
11:41:39 **that's listed specifically in the Z group of '7,803 claim,**
11:41:43 **is it?**
11:41:44 A. **It's actually within a bunch of them.**
11:41:47 Q. **It's not one of the ones that's specifically**
11:41:49 **identified; correct?**
11:41:50 A. **By itself, correct.**
11:41:51 Q. **And what it says at the bottom is, after the**
11:41:58 **acetylation that they reduced that agonistic activity,**
11:42:03 **right, which was a good thing. Right?**
11:42:06 A. **They reduced the histamine release. That was the good**
11:42:09 **thing.**
11:42:09 Q. **Well, but they also, they had some agonistic activity**
11:42:13 **with the acetylation?**
11:42:15 A. **They had the D-Arg for that.**
11:42:17 Q. **They added some other changes to get rid of that**
11:42:20 **problem; right?**
11:42:21 A. **Yes.**
11:42:21 Q. **But it doesn't say anything about getting rid of that**
11:42:24 **catecholamine release problem?**

11:42:26 A. **It does not speak to it.**

11:42:27 Q. **Now, let's look at Bodanszky. That's DTX-182. You also talked about Bodanszky; right?**

11:42:33 A. **Yes.**

11:42:35 Q. **Okay. That's at Page JTX-15.31, and I think there are two different exhibits of Bodanszky.**

11:42:35 **In your binder, DTX--- which -- you did DTX-182; is that correct, for Bodanszky?**

11:43:22 A. **I have it in your binder as, I have JTX-15.**

11:43:27 Q. **That will work. So we'll talk about JTX-15. If you turn to the page that in the lower right-hand corner has FKIA-0032178 on it, which I believe is JTX-15.31.**

11:43:31 A. **Yes.**

11:43:36 Q. **Okay. And you've pointed the Court to that paragraph at the bottom of the page; right?**

11:43:41 A. **Yes.**

11:43:45 Q. **And in that, the sentence that you focused on was, for instance, acetylation and benzoylation of amino groups is impractical. Right?**

11:43:55 A. **Right.**

11:43:55 Q. **And acetylation and benzoylation again means adding an acetyl group or a benzoyl group to these amino groups; right?**

11:43:58 A. **Yes. That's acylation.**

11:43:59 Q. **It says acetylation. It doesn't say acylation?**

11:44:00

11:44:07

11:44:11

11:44:13

11:44:13

11:44:17

11:44:21

11:44:22

11:44:25

11:44:29 A. **Right. I'm saying acylation is a general term for both of those things.**

11:44:32 Q. **Right. But this is a more specific term, acetylation and benzoylation?**

11:44:35 A. **Yes. Because it says, for instance. It's an example.**

11:44:36 Q. **But Fmoc is neither of those things, is it?**

11:44:39 A. **Not those two.**

11:44:41 Q. **And then, finally, you pointed the Court to the '204 patent; right? JTX-40?**

11:44:42 A. **Yes.**

11:44:51 Q. **And, in particular, you -- Mr. Chase, if you could pull up Column 3, lines 1 to 10.**

11:44:54 **And, Dr. Walensky, the paragraph at the top is what you brought to the Court's attention; is that right?**

11:45:04 A. **Yes.**

11:45:11 Q. **And there's a discussion of N-terminal protecting groups in that passage?**

11:45:15 A. **Yes.**

11:45:17 Q. **And there's no mention of Fmoc in that passage; right?**

11:45:18 A. **That's correct. It doesn't exclude them though, because it says, it is not limited to, and it lists them all, and actually, the verbiage for Fmoc is oxycarbonyl. You can see the Boc, the one after that, has the same**

11:45:18

11:45:23

11:45:24

11:45:25

11:45:29

11:45:30

11:45:32

11:45:35

11:45:40

11:45:44 **group.**

11:45:44 Q. **Well, Boc and Fmoc are different compounds?**

11:45:46 A. **I'm just saying in terms of the class, the**

11:45:48 **oxycarbonyls are listed there as examples.**

11:45:52 Q. **Again, it says at the end, it can be a D aminoacyl**

11:45:57 **residue?**

11:45:58 A. **You got it.**

11:46:02 Q. **And, again, the N protecting group here is in the**

11:46:05 **alternative, it can be this or that, one of these things;**

11:46:09 **right?**

11:46:09 A. **Yes, it does. It tells you that you can do it.**

11:46:13 Q. **Now, you've talked a little bit about the fact that**

11:46:25 **if you were to take off -- you can take that down,**

11:46:29 **Mr. Chase.**

11:46:29 **If you were to take off the Z and P group of the**

11:46:36 **'7,803 claim, or just look at the peptide that would be left**

11:46:38 **over, that you wouldn't expect it to be a bradykinin**

11:46:41 **antagonist; right?**

11:46:43 A. **If you took that in the context of the prior art and**

11:46:46 **you handed it to someone in January of 1989, then you would**

11:46:49 **not recognize that. That was my opinion.**

11:46:52 Q. **But it is your opinion that a person of skill in the**

11:46:55 **art would interpret the peptides of Claim 1 of the '7,803**

11:47:00 **patent to be bradykinin antagonists with modifications at**

11:47:04 **the N-terminus; right?**

11:47:07 A. '7,803?
11:47:08 Q. Yes.
11:47:08 A. If you read around -- if we're going outside the
11:47:11 specific language of the claim in the context, yes. I mean,
11:47:14 you have this patent with a title that says the bradykinin
11:47:16 antagonist with N-terminal modification.
11:47:19 Q. So you would only view it as a bradykinin antagonist
11:47:22 if you looked at the remainder of the claims of the patent.
11:47:26 Right?
11:47:26 A. I want to be clear. Are you asking me before 1989,
11:47:31 put in the context of the prior art or are you asking me
11:47:35 to look at them side by side? That's two different
11:47:37 questions.
11:47:43 Q. I think your testimony has been that you are offering
11:47:54 the opinion that you would view them as bradykinin
11:47:58 antagonists when you looked at the title and the
11:48:00 specification and the data in the patent. Right?
11:48:02 A. Yes, when I am analyzing the patent.
11:48:11 Q. Now, you also brought the Court's attention to Claim 2
11:48:16 of the '7,803 patent. Right?
11:48:18 A. Yes.
11:48:18 Q. And if we could put up Claim 2, just for context,
11:48:28 Claim 1 of the '7,803 patent doesn't say anything about
11:48:32 administering the compound. Right?
11:48:34 A. That's correct.

11:48:36 Q. **Claim 2 is a method claim. Correct?**
11:48:40 A. **Correct.**
11:48:41 Q. **And it's a method for the treatment of inflammation, et cetera, that's caused by bradykinin or peptides related to bradykinin, which comprises administering the peptide of the Formula I as claimed in Claim 1. Right?**
11:48:54 11:48:58 11:49:01 A. **Correct.**
11:49:01 Q. **And based on Claim 2, a person of skill in the art would understand that the peptides of Claim 1 had bradykinin antagonist activity. Right?**
11:49:08 11:49:13 11:49:14 A. **It doesn't say that in that, no. It says related to bradykinin. In terms of the explicit language, no, it doesn't say that in that language you just read.**
11:49:21 11:49:24 11:49:25 Q. **If you look at Claim 2, a person of skill in the art would understand that the peptide of the Formula I as claimed in Claim 1 was being used as a bradykinin antagonist?**
11:49:30 11:49:33 11:49:38 A. **They might intuit that. But I want to be clear that is not stated in that English language. They could interpret that for sure. But that's not said. It doesn't say bradykinin antagonist in Claim 2.**
11:49:38 11:49:42 11:49:44 11:49:47 Q. **Right. But a person of skill in the art would understand that that is what is being conveyed, that it's acting as a bradykinin antagonist. Correct?**
11:49:50 11:49:52 11:49:55 11:49:58 A. **If they were reading other things. If they were just**

11:50:01 **reading that, it doesn't really say what the purpose is. It**
11:50:03 **is just saying that it's going to treat inflammation. There**
11:50:06 **is lots of ways to treat inflammation.**
11:50:15 **MR. JAMES: Your Honor, if I could, I would like**
11:50:17 **to draw his attention to his deposition transcript.**
11:50:19 **THE COURT: Sure.**
11:50:20 **BY MR. JAMES:**
11:50:20 Q. **You have another binder up there with your deposition**
11:50:23 **transcript in it.**
11:50:24 A. **Sure.**
11:50:42 Q. **If you turn to Page 315, Line 19?**
11:51:22 A. **Yes.**
11:51:23 Q. **I asked you, "I'm just saying, if you look at Claim 2,**
11:51:30 **a person of skill in the art would understand that the**
11:51:32 **peptide of the Formula I as claimed in Claim 1 was being**
11:51:36 **used as a bradykinin antagonist, right?**
11:51:40 **"Answer: It doesn't say bradykinin antagonist."**
11:51:42 A. **That's what I just said.**
11:51:44 Q. **"Question: What would they understand it to be doing**
11:51:47 **if it was being given for the treatment of inflammation in**
11:51:50 **conditions that are mediated, induced or assisted by**
11:51:53 **bradykinin?**
11:51:54 **"Answer: Well, I'm just saying you could**
11:51:55 **interpret that. But I'm just saying if you want me to say**
11:51:58 **what's actually in there, it doesn't say the words**

11:52:01 **bradykinin antagonist, but you could have made that**
11:52:05 **interpretation.**
11:52:06 **"Question: That is the interpretation a person**
11:52:08 **of skill would make, correct?**
11:52:10 **"Answer: I'm just answering you yes."**
11:52:13 A. **Right. That's what I just said.**
11:52:17 Q. **So the person of skill in the art looking at Claim 2**
11:52:21 **would understand that the peptides of Claim 1 of the '7,803**
11:52:24 **patent were acting as bradykinin antagonists. That would be**
11:52:28 **the understanding they would have?**
11:52:29 A. **They could make that interpretation. But it doesn't**
11:52:31 **say it explicitly, that's all.**
11:52:33 Q. **So the D-Tic that's in the 7 position of Claim 1 of**
11:52:37 **the '7,803 patent didn't destroy the bradykinin antagonist**
11:52:42 **activity of that peptide, did it?**
11:52:44 A. **Are you asking me to answer that today or before 1989?**
11:52:47 **Because before 1989 there was no evidence of that.**
11:52:50 Q. **Doctor, you testified that the person of skill in the**
11:52:53 **art would understand the peptides of Claim 1 to act as a**
11:52:58 **bradykinin antagonist. Right?**
11:53:01 A. **I don't understand your question.**
11:53:03 Q. **In light of Claim 2, the person of skill in the art**
11:53:07 **would understand that the peptides of Claim 1 of the '7,803**
11:53:10 **patent were acting as bradykinin antagonists. I think we**
11:53:13 **just went through this.**

11:53:15 A. **If you have a retrospectroscope. But if you are**
11:53:18 **answering that before January of 1989 they would not have**
11:53:22 **recognized that as having a bradykinin antagonist --**
11:53:26 Q. **I don't know what that is, a retrospectroscope. I am**
11:53:30 **asking, if you are looking at Claim 2 and interpreting Claim**
11:53:34 **1 in view of Claim 2, you would understand that those**
11:53:37 **peptides would act as bradykinin antagonists?**
11:53:41 A. **If you were asking me today or asking me what a POSA**
11:53:44 **would interpret before January 1989, those are two different**
**answers.**
11:53:48 Q. **I am not asking you that. We are looking at the**
11:53:51 **'7,803 claims. Correct?**
11:53:53 A. **Correct.**
11:53:54 Q. **Regardless of the time frame, Claim 2 says to a person**
11:53:58 **of skill in the art that the peptides are acting as**
11:54:01 **bradykinin antagonists. Right?**
11:54:02 A. **If that was their interpretation.**
11:54:04 Q. **You said that was their interpretation.**
11:54:06 A. **I said it can be an interpretation.**
11:54:07 Q. **No. You said that would have been the interpretation**
11:54:10 **of the person of skill in the art. Right? Are you going to**
11:54:13 **take your testimony back?**
11:54:14 A. **I don't intend to. I am trying to explain to you that**
11:54:17 **if you were looking at that composition before 1989 you**
11:54:19 **would not recognize that as a bradykinin antagonist.**

11:54:22 Q. **I am not asking you about before 1989. I am just**
11:54:26 **saying, you are looking at the two claims together, the**
11:54:29 **person of skill in the art would understand that the**
11:54:31 **peptides of Claim 1 were acting as bradykinin antagonists?**
11:54:35 A. **Based upon looking at that patent.**
11:54:37 Q. **Based upon looking at Claim 2. Correct?**
11:54:40 A. **It doesn't explicitly state that. I don't know what**
11:54:43 **more you want me to say. There is a difference between**
11:54:47 **reading it and interpreting it.**
11:54:54 Q. **Okay. Now, let's look at PDX-3.22. This is a slide**
11:55:04 **that you put up in your direct examination. Correct?**
11:55:08 A. **Correct.**
11:55:08 Q. **And this shows, I think, what the title says is that**
11:55:14 **the person of skill in the art would have substituted the D**
11:55:17 **amino acids at Position 7. Right?**
11:55:20 A. **Correct.**
11:55:20 Q. **So in your view, the person of skill in the art**
11:55:25 **looking at the sequence of icatibant would have made the**
11:55:30 **substitutions that are laid out there for the '993 patent,**
11:55:33 **the '613 patent and the '963 patent. Right?**
11:55:37 A. **Correct.**
11:55:37 Q. **And -- let me ask you this: Why did you look at the**
11:55:42 **'993, the '613 and the '963 patents?**
11:55:45 A. **Because they are in the prior art and they are patents**
11:55:47 **that describe bradykinin antagonists.**

11:55:50 Q. **Right. You looked at them because you would have**
11:55:53 **understood that sequence to be a bradykinin antagonist?**
11:55:56 A. **No. Because that's what those patents said when I did**
11:55:59 **the search and pulled up patents that said here are**
11:56:03 **bradykinin antagonists that were reported before 1989.**
11:56:06 Q. **If we look at PDX-3.33, these are the substitutions**
11:56:14 **you say the person of skill in the art would have made at**
11:56:17 **the 8 position. Right?**
11:56:18 A. **Yes.**
11:56:18 Q. **And again, you looked at the '993 and the '963**
11:56:26 **patents. Right?**
11:56:27 A. **Yes.**
11:56:27 Q. **Those are Stewart patents related to bradykinin**
11:56:31 **antagonists. Right?**
11:56:33 A. **Right, dated before '89.**
11:56:34 Q. **Yes. I have made a slide where I put these two things**
11:56:37 **together, Slides 3.22 and 3.33, the sequence at the top is**
11:56:46 **icatibant. Right?**
11:56:48 A. **Yes.**
11:56:49 Q. **If you make at the 7 position the D-Phe substitution**
11:56:57 **for D-Tic. Right?**
11:56:59 A. **I wouldn't say you would, but if you wanted to do one.**
11:57:04 Q. **You said it was one of the preferred substitutions at**
11:57:06 **7. Right?**
11:57:08 A. **You are taking away the D-Tic and you are putting in**

11:57:11 **the D-Phe. Is that what you want me to do?**

11:57:13 Q. **I am asking you if that's what you said a person of**

11:57:17 **skill in the art would do, they would put in at the D-Tic**

11:57:20 **position, instead of using D-Tic, they would use one of**

11:57:23 **these amino acids as disclosed in the Stewart patents.**

11:57:25 **Right?**

11:57:26 A. **Right, and you are picking D-Phe.**

11:57:28 Q. **I am picking D-Phe.**

11:57:31 A. **Got it.**

11:57:31 Q. **If we put D-Phe there, and then if at the 8 position**

11:57:35 **from the '993 and the '963 patent, Thi I think was the first**

11:57:41 **option there. Right?**

11:57:41 A. **Yes.**

11:57:42 Q. **If we put that in for Oic, what we get is the sequence**

11:57:45 **of B-3824. Right?**

11:57:47 A. **Yes.**

11:57:47 Q. **So your opinion is a person of skill in the art would**

11:57:50 **look at the sequence of icatibant and go backwards to the**

11:57:53 **prior art?**

11:57:54 A. **It's not backwards. It's definitely not backwards.**

11:57:57 Q. **B-3824 was in the prior art. Right?**

11:58:00 A. **Right. But he would go to something that was familiar**

11:58:02 **and was recommended by the inventors.**

11:58:15 Q. **You talked a little bit about a Vavrek article in your**

11:58:20 **direct examination. Right?**

11:58:21 A. **Yes.**

11:58:22 Q. **If we could put that up, it's JTX-25. This is an article that's authorized by Stewart and Vavrek. Right?**

11:58:32 A. **Yes.**

11:58:36 Q. **This is that same Stewart group we have all been talking about in this case that was doing the work at the University of Colorado on BK antagonists. Right?**

11:58:36 A. **Yes.**

11:58:40 Q. **If we look at the table that you directed the Court's attention to -- I apologize -- Table 1 at the top of JTX-25.2, so we understand this table, this table is measuring agonist activity. Right?**

11:58:42 A. **Correct.**

11:58:45 Q. **That's why at the top, bradykinin has a proline at the 7, it has 100 for its measurement. Right?**

11:58:48 A. **That's correct.**

11:58:53 Q. **So everything else is normalized to that. Right?**

11:59:02 A. **Right.**

11:59:08 Q. **So everything else is compared to that to see whether or not it's working as an agonist or not. And you pointed the Court to, I think, tryptophan?**

11:59:11 A. **No. I just talked about D-phenylalanine and there are a bunch of D-aromatic amino acids there that didn't make it an antagonist.**

11:59:11 Q. **Let's look at tryptophan. Tryptophan takes it down to**

11:59:18

11:59:22

11:59:22

11:59:25

11:59:25

11:59:29

11:59:32

11:59:35

11:59:39

11:59:43

11:59:44

11:59:48 **4?**

11:59:48 A. **Yes.**

11:59:49 Q. **That is a 96-percent decrease?**

11:59:52 A. **Yep. Zero percent antagonist.**

11:59:54 Q. **This is from 1985, this paper. Right?**

11:59:58 A. **Yes.**

11:59:59 Q. **There was more known by 1989, like the '963 and the '993 patent. Right?**

12:00:05 A. **Correct.**

12:00:09 Q. **And tryptophan is an aromatic amino acid. Right?**

12:00:12 A. **It's a non-constrained aromatic amino acid, yes.**

12:00:15 Q. **If we could go to your Slide 3.19, in fact, Doctor, this is an excerpt from the '993 patent. Correct?**

12:00:36 A. **Correct.**

12:00:37 Q. **And the '993 patent again is authored by Stewart and Vavrek. Right?**

12:00:42 A. **Right.**

12:00:42 Q. **And you have shown the claim here, the claim, the Y is selected from the group comprising, that group that you have there, that is from Claim 17. Right?**

12:00:54 A. **Yes.**

12:00:54 Q. **And Claim 17 -- perhaps we should put it up on the screen if we could. It's the very last page, Mr. Chase.**

12:01:24 **On the right-hand side, Claim 17 is a modified bradykinin type peptide antagonist having the formula, and**

12:01:32 then there is a formula with a Y group. Right?
12:01:34 A. Yes.
12:01:35 Q. Y group at 7?
12:01:36 A. Yes.
12:01:37 Q. And so these are antagonists. Right?
12:01:39 A. They are now, with all the other changes in there,
12:01:42 yes.
12:01:42 Q. And one of the things they list there is D-tryptophan.
12:01:46 Right?
12:01:46 A. Right, but you can't --
12:01:48 Q. That was one of the examples that had agonist activity
12:01:53 in that table, but they are actually claiming it as an
12:01:56 antagonist. Right?
12:01:56 A. That proves my point. The point that I make there is
12:02:00 you can take -- this is basically a combination lock with
12:02:03 ten positions, and at each position you have all these
12:02:06 choices. And you are trying to spin your wheels at each
12:02:08 position to come up with an antagonist.
12:02:11 And you could put D-tryptophan in some peptides
12:02:14 where it is an antagonist and you can put D-tryptophan in
12:02:17 other peptides where it is an agonist. That is simply
12:02:21 because when you design peptides, what you do at one
12:02:23 position can be dramatically altered by what you do at the
other position.
12:02:25 I can show you peptides where D-tryptophan is

12:02:28 **good. I can show you peptides where D-tryptophan is bad.**

12:02:36 **You can make peptides where D-tryptophan in that**

12:02:39 **position is in the context of a good peptide.**

12:02:42 **You could put D-tryptophan in that same position**

12:02:45 **and have a peptide that is a bad peptide. That is because**

12:02:48 **you can't look at one position in isolation. What you do in**

12:02:52 **one position can be dramatically affected by what you do in**

12:02:55 **different positions.**

12:02:56 **Just because in one assay in one context it was**

12:02:59 **in a peptide that was an agonist, and then you could have**

12:03:02 **that exact same residue in the context of another peptide**

12:03:06 **sequence and it be an antagonist, that is the story of**

12:03:10 **peptide drug development.**

12:03:11 **This is a combination lock with ten different**

12:03:14 **wheels. And you are trying to find that combination among**

12:03:16 **1100-plus peptide positions and combinations to find the**

12:03:20 **winner.**

12:03:20 **What you do in one position doesn't mean it's**

12:03:22 **always going to give you an agonist. And what you do in**

12:03:25 **that position doesn't always mean you are going to get an**

12:03:28 **antagonist.**

12:03:28 **That is a really nice example of that.**

12:03:31 Q. **I have one last topic I would like to touch on with**

12:03:35 **you.**

12:03:36 **If you could turn in the '7,803 patent, Column**

12:03:40 **16, Lines 55 to 57?**

12:03:45 A. **What is the JTX again for that? 59?**

12:03:52 Q. **Yes. DTX.**

12:03:58 A. **What column?**

12:03:59 Q. **Column 16, Lines 55 to 57. Okay?**

12:04:13 A. **Okay.**

12:04:13 Q. **You see there that it says that the invention relates to the use of peptides of the Formula I as medicines and to pharmaceutical products which contain these compounds. Do you see that?**

12:04:26 A. **Yes.**

12:04:26 Q. **The peptides of Formula I, those are the ones that are claimed in Claim 1. Right?**

12:04:29 A. **Yes.**

12:04:31 Q. **And if you look at, just down below that, at Line 62 of Column 16, you see that it says that the administration of these -- I skipped over something. It says that the pharmaceutical products contain an effective amount of the active substance of Formula I, singly or in combination, together with an inorganic or organic pharmaceutically utilizable excipient.**

12:04:31 **Do you see that?**

12:04:43 A. **I do.**

12:04:48 Q. **That is saying that the compounds of Formula I can be formulated as pharmaceuticals. Right?**

12:04:51

12:04:56

12:04:58

12:05:01

12:05:02

12:05:02

12:05:05

12:05:07 A. **Yes.**

12:05:07 Q. **And then, if we look at Line 62, it says that you can administer these compounds enterally, that means by mouth. Right?**

12:05:18 A. **Yes.**

12:05:19 Q. **Parenterally, that means by injection. Right?**

12:05:22 A. **Yes.**

12:05:22 Q. **You can give them subcutaneously. Right?**

12:05:25 A. **Yes.**

12:05:25 Q. **Or intramuscularly?**

12:05:28 A. **Yes.**

12:05:28 Q. **Or intravenously?**

12:05:29 A. **Yes.**

12:05:30 Q. **And a lot of other ways. Right?**

12:05:33 A. **Yes.**

12:05:33 Q. **And then if we look at Column 17, Lines 1 to 3, it says that these pharmaceutical products are prepared, and it says in dissolving, mixing, granulating and coating processes known per se. Right?**

12:06:00 A. **Yes.**

12:06:00 Q. **And that's part of the formulation process. Right?**

12:06:04 A. **Yes.**

12:06:07 Q. **And then down below that, at Column 17, Lines 36 to 43?**

12:06:17 A. **Yes.**

12:06:17 Q. **It says, "For intravenous, subcutaneous, epicutaneous, or intradermal administration, the active compounds or the physiologically tolerated salts thereof are converted, if required, with the pharmaceutically customary ancillary substances, for example, for rendering isotonic or adjusting the pH, as well as solubilizers, emulsifiers or other ancillary substances, into a solution, suspension or emulsion."**

**Right?**

12:06:45 A. **Yes.**

12:06:46 Q. **That is just saying a person of skill in the art could formulate these products to administer in any way they wanted to. Right?**

12:06:52 A. **Yes. It's kind of stock patent language.**

12:07:09 **MR. JAMES: Your Honor, I have no further questions.**

12:07:12 **THE COURT: All right. Counsel.**

12:07:15 **MS. KUZMICH: Your Honor, a short redirect.**

12:07:26 **THE COURT: Yes.**

12:07:28 **REDIRECT EXAMINATION**

12:07:28 **BY MS. KUZMICH:**

12:07:29 Q. **Mr. Chase, if you could please put up, I think the demonstrative was DDX-5.2, it was the Fmoc-icatibant to icatibant.**

12:07:41 **Thank you.**

12:07:43 **Dr. Walensky, Mr. James asked you a question earlier about interpreting his schematic at the top for the icatibant and then the Fmoc-icatibant. Just so we are clear, before I continue, I believe you and Mr. James agreed that the bottom peptide was Fmoc-icatibant where it was not on the resin and it had no side chain protecting groups. Is that correct?**

A. **Yes. That's where we found an agreement.**

Q. **Okay. Thank you, Mr. Chase.**

**I am going to switch to the slides. Ms. Debonis, would you please bring up DTX-60.**

**If we could turn to the scheme that Mr. James brought up, DTX-60, Page 4, we also have that on the screen, but it would be in the binder that Mr. James gave you?**

A. **I have it.**

Q. **My first question is: The arrow, the first arrow that you see moving down up to the 23 cycles --**

A. **Yes.**

Q. **-- when Fmoc was removed each time, was that peptide on the resin?**

A. **Yes.**

Q. **And each time that Fmoc was removed, was there a protecting group on that peptide?**

A. **Yes.**

Q. **And then if you take a look at the next arrow down,**

12:09:06 **under those conditions, when the peptide was treated with**
12:09:09 **20 percent piperidine, did that remove the Fmoc?**
12:09:12 A. **It should.**
12:09:13 Q. **When that reaction was done, was the peptide on the**
12:09:17 **resin?**
12:09:17 A. **Yes.**
12:09:18 Q. **When that reaction was done, were the side chain**
12:09:21 **protecting groups on the peptide?**
12:09:22 A. **Yes.**
12:09:22 Q. **And how does that condition differ, or how does the**
12:09:27 **peptide structure differ when Fmoc was removed as compared**
12:09:32 **to the schematic that you and Mr. James agreed on?**
12:09:35 A. **He was asking me about removing Fmoc from a pure**
12:09:38 **product. The scheme he took me to was removing Fmoc from a**
12:09:44 **peptide under construction on the resin with protecting**
12:09:45 **groups in place.**
12:09:46 Q. **And if you could bring up JTX-39, please, and turn to**
12:09:59 **Table 5 at JTX-39.11. And if you would please highlight the**
12:10:11 **peptide that is the seventh peptide down. It has the N acyl**
12:10:17 **or acetyl group on that. Thank you.**
12:10:19 **Dr. Walensky, do you have that in front of you?**
12:10:22 A. **Yes.**
12:10:22 Q. **And would you please explain the structure at that**
12:10:26 **peptide at the N-terminus?**
12:10:28 A. **It has an acetyl group sitting on top of the**

12:10:33 **D-arginine. So it's basically an acylated or acetylated**
12:10:37 **D-arginine. So there's an N-terminal protection group on**
12:10:41 **the D-arginine itself.**
12:10:43 Q. **And would you please bring up JTX-40 and turn to**
12:10:50 **Column 3, lines 1 through 10, and highlight that on the**
12:10:56 **screen, please.**
12:10:59 **And, Dr. Walensky, I turn your attention to the**
12:11:02 **very last part of Column 1 to 10, which is about columns, or**
12:11:10 **lines 8 through 9, excuse me.**
12:11:12 **And what does it mean when it says, which may**
12:11:15 **itself be N protected similarly? How does a person of**
12:11:19 **ordinary skill in the art interpret that?**
12:11:21 A. **That they can acetylate or acylate or put any other**
12:11:25 **chemical modification onto the N-terminus of that D-arginine**
12:11:29 **residue.**
12:11:31 **MS. KUZMICH: No further questions, Your Honor.**
12:11:32 **THE COURT: Doctor, thank you. Be careful**
12:11:34 **stepping down there.**
12:11:36 **(Witness excused.)**
12:11:37 **THE COURT: I think this would be a good time**
12:11:38 **for lunch. Let's take an hour.**
12:11:40 **(Luncheon recess taken.)**
13:12:48 **- - -**
13:12:48 **Afternoon Session - 1:12 p.m.**
13:12:49 **THE COURT: All right, counsel. Please take**

13:12:50 your seats. Let's resume.

13:12:58 Mr. Haug?

13:13:00 MR. HAUG: Good afternoon, Your Honor.

13:13:01 THE COURT: Good afternoon.

13:13:02 MR. HAUG: The next witness that the plaintiffs
13:13:04 will call by, presented by deposition, will be Dr. Kyle,
13:13:10 Donald Kyle, who was employed at Nova Pharmaceutical
13:13:15 beginning in 1986, and Dr. Kyle was research team leader of
13:13:21 the kinin antagonist program at Nova from 1990 to '95 and
13:13:26 director of medicinal chemistry.

13:13:28 And I think the clip is about one hour.

13:13:37 THE COURT: All right. Do you have a
13:13:38 transcript?

13:13:38 MR. HAUG: Yes, we do.

13:14:04 (The videotaped deposition of Donald Kyle was
13:14:06 played as follows.)

13:14:08 "Question: Would you please state your full
13:14:10 name for the record.

13:14:10 "Answer: Yes. My name is Donald James Kyle.

13:14:13 "Question: And what is your current address?

13:14:34 "Answer: 173 North Main Street in Yardley,
13:14:36 Pennsylvania.

13:14:37 "Question: Is there any reason why you can't
13:14:43 testify fully and completely today?

13:14:45 "Answer. No.

13:14:46 "Question: Is there any reason why you can't
13:14:50 testify truthfully today?
13:14:52 "Answer: No.
13:14:55 "MS. KUZMICH: This is going to be marked,
13:14:57 again, as Kyle Exhibit 3. Thank you. Will.
13:15:01 "(Kyle Exhibit 3, curriculum vitae, marked for
13:15:07 identification).
13:15:07 "Question: So if you would take a moment, Dr.
13:15:10 Kyle, and take a look at Exhibit 3, and it is marked as
13:15:14 Bates numbers Kyle 000032 to Kyle 000066.
13:15:24 "Answer: Okay.
13:15:25 "Question: Do you recognize this document, Dr.
13:15:30 Kyle?
"Answer: Yes.
13:15:32 "Question: What is this document?
13:15:34 "Answer: It looks like my resumé.
13:15:36 "Question: It looks like in 1986, you received
13:15:42 a Ph.D. in chemistry from Texas Tech University.
13:15:47 "Is that correct?
13:15:49 "Answer: That's correct.
13:15:49 "Question: Did you receive a Ph.D. in any
13:15:52 particular field of chemistry?
"Answer: Yes.
13:15:55 "Question: What was that field?
13:15:58 "Answer: Synthetic organic chemistry.

13:16:01 "Question: And if look at your resumé, it
13:16:03 appears that in 1986, you received your Ph.D. and then you
13:16:11 also began what appears to be an employment with the company
13:16:17 Nova Pharmaceutical Corporation; is that correct?
13:16:19 "Answer: That's right.
13:16:20 "Question: Dr. Kyle, the company that I see on
13:16:25 your resumé that's called Nova Pharmaceutical Corporation,
13:16:33 is it acceptable to you if today we just refer to that
13:16:37 company as Nova?
"Answer: Yes.
13:16:42 "Question: Your resume, which is Exhibit 3,
13:16:45 indicates that from 1986 to 1988, your title was research
13:16:51 associate medicinal chemistry; is that correct?
"Answer: Yes.
13:16:55 "Question: So what were your job
13:16:57 responsibilities as a research associate when you started
13:17:01 with Nova in 1986?
13:17:03 "Answer: I was one of several chemists working
13:17:08 in the laboratory synthesizing molecules, you know, and
13:17:15 synthesizing, purifying, analyzing for, you know, proper
13:17:19 purity and structure proof, molecules as potential
13:17:26 therapeutic agents that would be handed off to our
13:17:29 pharmacologist in the company for various types of in vitro
13:17:34 and in vivo testing.
13:17:36 "Question: So before we talk about your title

13:17:39 as director of medicinal chemistry, there's another entry on
13:17:44 your resume that says from 1990 to 1995 --
13:17:49 "Answer: Yeah.
13:17:51 "Question: -- you were research team leader
13:17:54 kinin antagonist. Do you see that?
"Answer: Yes.
13:17:57 "Question: So what was the job responsibility
13:18:01 in 1990 of research team leader kinin antagonist?
13:18:09 "Answer: There could have been more than one
13:18:10 research team leader, you know, the way things were set up.
13:18:13 My specific role was to lead the chemistry, the
13:18:19 design synthesis of compounds for the kinin program.
13:18:24 "Question: Thank you. So on your resumé, when
13:18:28 it says 'research team leader kinin antagonist,' was the
13:18:32 kinin antagonist a particular program at Nova?
"Answer: Yes.
13:18:38 "Question: And what was the objective of the
13:18:39 kinin antagonist program as of 1990 when you became research
13:18:49 team leader?
13:18:50 "Answer: Well, there was sort of two prongs to
13:18:54 the program. There was a lead part of the project that was
13:18:59 developing a lead compound in clinical -- in early clinical
13:19:03 trials. And then the part that I was more associated with
13:19:07 was the search for an alternative second-generation compound
13:19:14 that could have improved properties.

13:19:21 "Question: When you talk about a second
13:19:33 generation compound, are you referring to bradykinin
13:19:38 antagonist s?
"Answer: Yes.
13:19:40 "Question: What is your definition of a
13:19:43 bradykinin antagonist?
13:19:45 "Answer: That is a molecule that binds to the
13:19:53 bradykinin receptor and stabilizes a conformation of the
13:19:58 receptor that will not signal. So it basically shuts the
13:20:02 receptor off, blocks the action of the endogenous agonist.
13:20:10 "Question: You said that there were two prongs
13:20:13 to the kinin project.
13:20:16 "Answer: Yes.
13:20:17 "Question: And the first one was moving
13:20:18 forward, I guess, with the lead compound, clinical phase?
13:20:22 "Answer: Yeah.
13:20:23 "Question: And the second one was where you
13:20:25 were more involved for -- searching for an alternative
13:20:29 second generation product with better properties?
13:20:32 "Answer: Yes.
13:20:48 "Question: Were both of those projects, though,
13:20:53 involving bradykinin antagonists?
13:20:55 "Answer: Yes.
13:20:55 "Question: Your resume also defines you as from
13:21:01 1992 to 1995 director of medicinal chemistry.

13:21:08 "Do you see that?

13:21:10 "Answer: Uh-huh. Yes.

13:21:12 "Question: So when you described the two prongs of the kinin antagonist project --

13:21:18

13:21:21 "Answer: Yes.

13:21:22 "Question: -- is it the case that where you were focused was the chemistry and coming up with a second generation lead compound and further?

13:21:26

13:21:29

13:21:40 "Answer: Yes.

13:21:40 "Question: At any point in time in your career from when you started at Nova in 1986 to leaving Scios in '98, was there a termination of the bradykinin antagonist program?

13:21:42

13:21:50

13:21:56

13:21:56 "Answer: Actually, I don't recall if there was a 'hard' termination of the program.

13:21:59

13:22:03 "Question: Would you say throughout your time at Nova much of your work was involved in the bradykinin antagonist program?

13:22:06

13:22:11

13:22:12 "Answer: Probably, yeah, a significant amount of time.

13:22:14

13:22:18 "Question: Did Dr. Steranka have involvement in the bradykinin antagonist program?

13:22:23

13:22:25 "Answer: I mean, as the head of research, you know, yes.

13:22:28

13:22:29 "Question: At any point did you report directly

13:22:33 to Dr. Enna?

13:22:35 "Answer: No.

13:22:36 "Question: Was Dr. Burch at Nova when you were there?

13:22:40

13:22:40 "Answer: Yes.

13:22:41 "Question: What was Dr. Burch's role at Nova?

13:22:50 "Answer: I think he was the head of pharmacology.

13:22:52

13:22:53 "Question: Did you work with Dr. Burch on the bradykinin antagonist program?

13:22:59

13:23:06 "Answer: Yes. I learned a lot from him.

13:23:09 "Question: Do you recall at meetings that you went to, say, while you were at Nova, meetings where Hoechst was presenting on their bradykinin antagonist program?

13:23:11

13:23:18

13:23:22 "Answer: No.

13:23:23 "Question: Do you know if there was any formal agreement between Hoechst and Nova to work on bradykinin antagonist compounds?

13:23:33

13:23:41

13:23:47 "Answer: I'm unaware of any agreement like that between Nova and Hoechst.

13:23:51

13:23:58 "Question: When you were working at Nova, did anyone from Hoechst -- strike that.

13:24:09 "When you were working at Nova, do you recall anyone at Hoechst coming to Nova and visiting Nova's facilities?

13:24:12

13:24:15

13:24:19

13:24:20 "Answer: No.

13:24:24 "Question: Do you know if anyone at Nova
13:24:27 visited Hoechst during the time frame that you were working
13:24:36 at Nova to discuss the bradykinin antagonist program?

13:24:50 "Answer: I don't know anybody who did that.

13:24:52 "Question: Did you consider Hoechst a
13:24:54 competitor in the bradykinin antagonist field?

13:24:59 "Answer: Not really. Yeah, not really.

13:25:02 "Question: Why not?

13:25:06 "Answer: I mean, I personally worked in the
13:25:11 bradykinin field, you know, for a number of years, you know,
13:25:15 starting fairly early on in my time at Nova. And, you know,
13:25:20 I was reading -- I mentioned earlier, you know, I was
13:25:24 reading the literature. I was searching, you know, things
13:25:29 and going to conferences and being an active member of sort
13:25:33 of the scientific peer process, and I never saw them there.

13:25:37 "I mean, like the competitor -- you asked me
13:25:40 earlier who some of the other players in the field were. I
13:25:45 knew that, because it was a small group and we were all sort
13:25:48 of attending regularly at conferences and you'd see the same
13:25:52 presenters. And there was nobody really from Hoechst in
13:25:56 that group, you know.

13:25:57 "Many, many years later, you know, when they
13:26:02 started publishing on their compound, then I became aware
13:26:05 that, you know, they had a bradykinin program, and -- but I

13:26:10 still didn't really view it as a competitor because I was
13:26:13 more interested in a second-generation better type of a
13:26:17 compound than, you know, these first -- what I would
13:26:21 consider to be these first-generation molecules. So my
13:26:28 focus was really changing -- you know, changing the first
13:26:32 generation into the second generation.
13:26:39 "Question: While you were at Nova working in
13:26:41 the bradykinin antagonist field, was there anything that
13:26:44 Hoechst did with respect to their work that impacted the
13:26:47 direction of Nova's bradykinin antagonist research?
13:27:05 "Answer: No, not that I recall.
13:27:09 "Question: Do you recall if any of the patents
13:27:11 that were issued in the bradykinin antagonist field while
13:27:14 you were at Nova impacted the direction of your bradykinin
13:27:17 antagonist work?
13:27:19 "Answer: Not really, no.
13:27:20 "Question: When you say 'Not really,' was there
13:27:26 something that you do recall about a competitor's patent?
13:27:34 "Answer: No. I'm sorry; I didn't mean not
13:27:37 really. I mean no.
13:27:39 "I felt like I was a pioneer, you know. So
13:27:43 there weren't a lot of other things in the literature that
13:27:46 were influencing me because there wasn't much there.
13:27:58 "Ms. Kuzmich: We're going to mark what is going
13:28:03 to be Kyle Exhibit 6, and that's going to be the 1989 annual

13:28:11 report from Nova, and it's marked with Bates numbers Kyle
13:28:19 000319 to Kyle 000352.
13:28:27 "Once again, I would ask you, Dr. Kyle, if you
13:28:32 could just take a look at this document and tell me if you
13:28:35 recognize the document?
13:28:36 "Answer: Yes, I do.
13:28:37 "Question: And what is the document?
13:28:42 "Answer: It's the Nova 1989 annual report.
13:28:46 "Question: Dr. Kyle, if you could turn to Page
13:28:50 322. It's 000322?
13:28:54 "Answer: Okay.
13:28:55 "Question: And on the right-hand column there
13:29:01 is a subsection entitled 'pain and inflammation.'
13:29:08 "Do you see that?
13:29:10 "Answer: Yes.
13:29:10 "Question: And then right before the bottom of
13:29:15 that column where the new paragraph starts, there's a last
13:29:22 sentence:
13:29:24 "Although the common cold trials with NPC567
13:29:30 were ended in Phase II, we are continuing our research in
13:29:33 this field and expect to develop compounds with greater
13:29:36 potency.'
13:29:38 "My first question is the lead compound that you
13:29:41 had been referring to earlier on in clinical trials, is that
13:29:46 NPC567?

13:29:48 "Answer: Yes, it is.

13:29:53 "Question: In trying to develop another lead
13:29:59 compound after NPC567, what were the properties of that
13:30:06 compound that you were looking for?

13:30:10 "Answer: Generally looking for high affinity
13:30:13 binding to the receptor, good metabolic stability so it
13:30:21 could have a long half-life and properties that would
13:30:28 ideally make it orally bioavailable.

13:30:34 "Question: I guess now putting aside the time
13:30:42 frame, I guess looking now at any time while you were at
13:30:46 Nova, do you recall that your group had synthesized
13:30:52 bradykinin antagonists that were much more potent than
13:30:58 NPC-567?

13:30:59 "Answer: Yes.

13:31:00 "Question: Do you recall what structure those
13:31:03 compounds had generally?

13:31:05 "Answer: Generally, yes.

13:31:06 "Question: What was that structure that those
13:31:11 compounds had generally?

13:31:19 "Answer: What was the structure?

13:31:21 "Question: Yeah.

13:31:22 "Answer: So, again, just backing up to what we
13:31:24 talked about earlier, my group, you know, from the beginning
13:31:28 was taking very much of a structure-based drug design
13:31:31 approach that started with the analysis of 'now I'm just

13:31:37 going to call it NPC567 the antagonist but also bradykinin,
13:31:42 you know, the endogenous agonist.'
13:31:46 "So we did NMR work and computational work to
13:31:50 look at what we believed was the three-dimensional
13:31:54 conformation or structure of those peptides that we felt
13:31:57 were the most relevant for high affinity binding to the
13:32:01 receptor.
13:32:02 "Subsequent peptides that we were making were
13:32:06 deliberately prepared to introduce what we would call
13:32:10 conformational constraints or chemical structural
13:32:13 modifications that limit the flexibility of the peptide, if
13:32:17 that makes sense to you.
13:32:18 "Question: Yes.
13:32:22 "Answer: And the goal -- our goal was to try to
13:32:25 find limitations or to restrict the conformation of the
13:32:28 peptide to be highly preferential for what we thought the
13:32:35 receptor bound state should be, and there was a certain
13:32:38 structural motif that we were after.
13:32:42 "And as we began to move into certain
13:32:46 conformational constraints in the key area of the molecule,
13:32:49 that's when we began to identify, you know, changes in the
13:32:52 potency of the compounds.
13:32:54 "Question: And so do you recall what generally
13:32:58 those structures were that gave you the compounds with
13:33:02 better potency?

13:33:05 "Answer: Yes.

13:33:06 "Question: What were they?

13:33:16 "Answer: What were the structures?

13:33:18 "Question: Yeah, generally.

13:33:19 "Answer: I mean, how do you want me to explain that to you?

13:33:22 "Question: Well, I think you were talking about how you were focused on the part of the molecule that seemed I'm going to say more relevant --

13:33:30 "Answer: Yes.

13:33:30 "Question: -- and talked about the conformational constraints. And so can you describe to me in general what those compounds looked like in that part of the antagonist that was more potent.

13:33:49 "Answer: Yeah. So our hypothesis, you know, from the NMR work was that -- and I'm going to call it the C-terminal end of the peptide. Is that okay for you?

13:34:01 "Question: Yes.

13:34:01 "Answer: Our hypothesis was that at the C-terminal end of the peptide, specifically the last four residues at the C-terminus, that there was a turn structure there known as a beta-turn.

13:34:13 "And when we started introducing conformational constraints into the -- really into the only two places where you can put conformational constraints in an amino

13:34:25 acid -- that's either in the backbone or in the side
13:34:27 chain -- and the types of constraints that would favor the
13:34:31 formation of a beta-turn structure, those are the types of
13:34:35 constraints that we were putting there, side chain and
13:34:38 backbone modifications particularly at Position 7 and 8
13:34:42 which would be the two center positions of the beta-turn.
13:34:46 "Question: Beta-turn.
13:34:48 "Do you recall in particular what types of amino
13:35:01 acids you were putting into Position 7 and 8 of the molecule
13:35:05 to give you that beta-turn that gave you an antagonist that
13:35:12 was more potent than in NPC567?
13:35:15 "Answer: Some.
13:35:16 "Question: Which ones do you recall?
13:35:20 "Answer: I recall the correct chemical name for
13:35:22 one of them is tetrahydroisoquinoline carboxylic acid. The
13:35:29 acronym is TIQ.
13:35:31 "John Stewart had previously shown through this
13:35:36 NPC567 that a D-amino acid configuration at Position 7 was
13:35:41 preferential for antagonism, and our NMR studies -- you
13:35:45 know, through our NMR studies, we had proposed the different
13:35:49 types of beta-turns based on that configuration would be
13:35:55 important to differentiate agonism versus antagonism, and
13:36:00 there is some publications that explain some of that.
13:36:06 "So putting the D isomer of TIQ into Position 7
13:36:10 is one of the changes. Also, the natural position at --

13:36:14 sorry, it's been a long time on the sequence -- but the
13:36:18 natural position at 8 in bradykinin is a phenylalanine.
13:36:24 Phenylalanine is very, very similar to a TIQ residue, one
13:36:30 carbon different but conformationally constrained. So
13:36:34 putting TIQ at Position 7 and 8 is one combination.
13:36:39 "We also used what we called ethers of
13:36:43 hydroxyproline for structural purposes, also kind of
13:36:47 interesting because they are non-aromatic amino acid -- it's
13:36:52 a non-aromatic amino acid, and prior to that there were no
13:36:56 examples of non-aromatic amino acids, you know, in the
13:36:59 literature. So it's another conformationally constrained
13:37:04 amino acid with a side chain.
13:37:07 "So those are probably the most significant
13:37:09 building block pieces that I recall.
13:37:11 "Question: Dr. Kyle, I'm going to have the
13:37:14 court reporter mark what is going to be Kyle Exhibit 8, and
13:37:25 it is a book chapter titled 'Conformational Properties of
13:37:33 Bradykinin and Bradykinin Antagonists,' and it's marked with
13:37:37 Bates numbers Kyle 000122 to Kyle 000130.
13:37:50 "Dr. Kyle, if you could just take a moment to
13:38:01 take a look at that exhibit and tell me if you recognize it.
13:38:05 "Answer: Yes, I do.
13:38:06 "Question: And what do you recognize it as?
13:38:09 "Answer: It's a chapter that I wrote with these
13:38:12 co-authors that are listed as part of a book that was edited

13:38:16 by Ron Burch. It had multiple chapters, and this is one
13:38:21 chapter out of the book.
13:38:23 "Question: So the very last sentence of Page
13:38:28 134 states, 'Although bradykinin has been the subject of
13:38:34 intensive investigations over the past 20 years,
13:38:38 surprisingly little is known about its mechanisms of action
13:38:42 at the molecular level.'
13:38:44 "Do you see that?
13:38:45 "Answer: Yes.
13:38:45 "Question: What is meant by that statement?
13:38:49 "Answer: 'Mechanism of action at the molecular
13:38:52 level.' It's similar to what I was describing earlier. You
13:38:56 know, bradykinin is a 9 amino acid residue peptide, and it
13:39:03 conceivably could exist in a lot of different conformational
13:39:06 states.
13:39:07 "Which one is the one that binds to the receptor
13:39:11 and where is it binding, which amino acids in the receptor
13:39:15 are holding it in place, you know, what are the key contact
13:39:19 points, what is the electrostatic interactions, you know,
13:39:23 that are holding it in place -- that's the -- that's what's
13:39:27 meant by mechanism of action at the molecular level. How
13:39:32 and why and where does bradykinin bind to its receptor.
13:39:36 "Question: And I guess what is being stated
13:39:37 here is that there's surprisingly little known before those
13:39:43 aspects of bradykinin.

13:39:45 "Answer: That's right. At the time of this,
13:39:48 yes.
13:39:48 "Question: That paragraph that's at the top of
13:39:53 Page 135, it talks a little bit about conformationally
13:40:02 constrained analogs of bradykinin that have been prepared
13:40:08 and tested --
13:40:18 "Answer: Yes.
13:40:18 "Question: -- that are mostly weak or inactive
13:40:22 agonists. Do you see that?
13:40:23 "Answer: Yes.
13:40:24 "Question: There's a sentence that follows the
13:40:28 structure of NPC567 in that paragraph, and it states: 'As
13:40:36 one approach toward understanding the conformational
13:40:39 differences between NPC567 and bradykinin, we are pursuing
13:40:45 an examination of this antagonist in a fashion similar to
13:40:49 that described previously for bradykinin.'
13:40:53 "Do you see that?
13:40:55 "Answer: Yes.
13:40:55 "Question: Can you describe what those studies
13:40:57 were?
13:40:58 "Answer: That we were pursuing?
13:41:04 "Question: Yes.
13:41:06 "Answer: Some of them are described in what
13:41:09 comes next in that paragraph. That's the primary beginning
13:41:13 of the work. It's using NMR spectroscopy, specific

13:41:20 **experiments, you know, multi-dimensional experiments in NMR**
13:41:26 **spectroscopy to measure distance through space, distances**
13:41:30 **between hydrogen atoms in the protein and then using those**
13:41:36 **distances in computer simulations to figure out what the**
13:41:45 **conformation of the three-dimensional structure is. And so**
13:41:53 **that -- that is some of what he tells -- that -- that is**
13:41:59 **some of what's talking -- what's being talked about there.**
13:41:20 **"Question: Was this the first publication of**
13:41:49 **your work regarding this type of studies on the conformation**
13:41:52 **of NPC567?**
**"Answer: Yes.**
13:41:59 **"Question: So when Dr. Stewart and Vavrek were**
13:42:02 **designing, however they did, NPC567, they didn't have the**
13:42:06 **benefit of what you were doing here; is that correct?**
13:42:09 **"Answer: No -- oh, sorry.**
13:42:13 **Yeah. No, they did not. They were taking a**
13:42:17 **different approach.**
13:42:17 **"Question: Dr. Kyle, we're going to mark what's**
13:42:20 **going to be Kyle Exhibit 9, and it's an article titled,**
13:42:34 **'D-Arg[Hyp3,Thi5,D-Tic7,Tic8]-bradykinin, a potent**
13:42:35 **antagonist of smooth muscle BK2 receptors and BK3 three**
13:42:39 **receptors.'**
13:42:40 **"Answer: Okay.**
13:42:41 **"Question: That's Kyle Exhibit 9.**
13:42:43 **"Answer: Okay. Got it.**

13:42:44 (Kyle Exhibit 9, article titled,
13:42:47 D-Arg[Hyp3-Thi5-D-Tic7-Tic8]-bradykinin, a potent antagonist
13:42:54 of smooth muscle BK2 receptors and BK3 receptors,' marked
13:42:59 for identification.)
13:43:01 "Question: Do you recognize this publication,
13:43:03 Dr. Kyle?
13:43:04 "Answer: I mean, I'm an author on the
13:43:06 publication from 1991. So, you know, yes, I recognize it in
13:43:10 general terms, but, you know, it's been a long time since
13:43:13 I've looked at this.
13:43:14 "Question: And so I was asking more along the
13:43:16 lines of how did the actual peptide sequence of 16731 come
13:43:21 about?
13:43:22 "Answer: You mean, how was it designed, or
13:43:24 where did we come from it, or where did we get it?
13:43:28 "Question: Yeah, how did that sequence come
13:43:30 about? I mean, who -- who chose it? On what basis? Do you
13:43:41 have any recollection?
13:43:42 "Answer: I mean, not specifically, but just in
13:43:44 general, it incorporates things that we've been talking
13:43:47 about, so far, you know.
13:44:04 So, I mean, starting at the N-terminal end, the
13:44:08 D-Arg -- my memory is that's kind of a holdover from some of
13:44:14 John Stewart's earlier work. He started putting a D-Arg at
13:44:19 the N-terminus but the D amino acid would be more stable

13:44:23 against enzymatic degradation. As a D amino acid, it's not
13:44:30 recognized by the enzyme. So D-Arg is there for that
13:44:33 reason.
13:44:33 "In the sequence of bradykinin, that third
13:44:36 position is proline. It's not hydroxyproline. And I think
13:44:47 that's another John Stewart -- John Stewart made a lot of
13:44:50 analogs over a long period of time of just changing amino
13:44:53 acids in the sequence.
13:44:54 So putting a hydroxyproline over there, you
13:45:01 know, he had reasons for that. I don't remember what they
13:45:03 were, and I don't remember how significant they were. It
13:45:05 seems like sometimes in our peptides when we were taking
13:45:09 things, we'd put it in and sometimes we didn't put it in,
13:45:12 but I don't really remember much about that.
13:45:14 "The thienylalanine at position five, I'm not a
13:45:18 hundred percent sure, but I kind of remember that that's
13:45:22 also something that John Stewart had also worked on. That's
13:45:24 kind of a mimic of phenylalanine.
13:45:32 "Phenylalanine has a six-membered aromatic
13:45:37 phenyl ring in its side chain connected by one carbon to the
13:45:41 backbone alpha carbon. Thienylalanine is exactly the same
13:45:45 except it's only a five membered ring and it has sulfur in
13:45:48 it, but it's still aromatic. And so it's a little bit
13:45:52 smaller, and the aromaticity is a little more robust.
13:45:55 "And so that's also something that John

13:45:57 **Stewart -- you know, that's a holdover from his and that we**
13:46:01 **use that from time to time as well.**
13:46:02 **"The D-Tic, that's a conformationally**
13:46:06 **constrained D-phenylalanine at position seven. The side**
13:46:10 **chain is constrained from rotation because it's tied back to**
13:46:13 **the backbone, and by tying it to the backbone, then one of**
13:46:17 **the backbone dihedrals is also constrained.**
13:46:21 **So D-Tic7 and Tic8 are a pair of amino acids**
13:46:28 **basically mimicking phenylalanine but with conformational**
13:46:32 **constraints that, you know, we had reason to believe gave us**
13:46:35 **the beta-turn -- preferential beta turn structure that we**
13:46:40 **had seen previously by NMR.**
13:46:44 **Question: So --**
13:46:46 **"Answer: And then -- I'm sorry. And then,**
13:46:49 **yeah, the last residue would be the arginine at the**
13:46:52 **c-terminus.**
13:46:53 **"Question: So --**
13:46:54 **"Answer: So it's designed -- I'm sorry. So it**
13:46:56 **comes out of our -- it comes out of our structure based, you**
13:47:00 **know, approach building on the book chapter NMR work.**
13:47:08 **C terminal beta-turn is important for binding,**
13:47:12 **and we were going through a lot of work to figure out**
13:47:14 **what kinds of amino acids to put in there, too, to impose**
13:47:18 **that.**
13:47:18 **"Question: So the replacement in the 7 and 8**

13:47:20 positions of D-Tic and Tic respectively reflects what came
13:47:25 out of your work that we talked about in the previous
13:47:28 exhibit; is that correct?
"Answer: Yes.
13:47:30 "Question: If you look at Page 7 87, at the
13:47:32 very bottom on the right-hand side, it says, 'Received
13:47:36 October 26, 1990.'
13:47:38 "Do you see that?
13:47:39 "Answer: Did you say 787?
13:47:41 "Question: Yeah, 787, the next page at the
13:47:44 top:
13:47:45 "Answer: Yes.
13:47:46 "Question: Was this work then conducted prior
13:47:48 to October 26, 1990?
13:47:50 "Answer: Yes, it must have been.
13:47:52 "Question: Do you have any idea when this work
13:47:54 began, this study that's reported in what's marked as Kyle
13:47:57 Exhibit 9?
13:47:58 "Answer: I mean, definitely before October
13:48:01 the 26th of 1990, but I mean, other than that, I'm really
13:48:04 not sure.
13:48:04 "Question: Okay.
13:48:05 "Answer: You know, there's quite a bit of work
13:48:07 reported in this pharmacology work in that it takes time.
13:48:11 So, you know, there would have been some time to generate

13:48:14 **the data and all that, so. But it's unknown what the time**
13:48:18 **is.**
13:48:18 **"Question: So, Dr. Kyle, we're going to mark as**
13:48:23 **what's going to be Kyle Exhibit 10, and it was produced to**
13:48:26 **us as Kyle 000162 to Kyle 000166.**
13:48:32 **"Answer: Okay.**
13:48:33 **"Question: It's a paper titled, 'Design and**
13:48:37 **conformational analysis of several highly potent bradykinin**
13:48:40 **receptor antagonists.'**
13:48:43 **"(Kyle Exhibit 10, paper titled design and**
13:48:49 **conformational analysis of several highly potent bradykinin**
13:48:53 **receptor antagonists, marked for identification.)**
13:48:57 **"Question: And, Dr. Kyle, if you could just**
13:48:59 **take a look at it and let me know if you recognize this**
13:49:01 **document.**
13:49:02 **"Answer: I do.**
13:49:03 **"Question: Is it the case if you look back on**
13:49:08 **Page 1233, the last page of the article, Dr. Kyle, it says**
13:49:12 **the article was received on December 10, 1990.**
13:49:15 **"Does that mean that the work that's described**
13:49:18 **in this article would have been completed by that date?**
**"Answer: Yes.**
13:49:22 **"Question: So if you could turn back to Kyle**
13:49:23 **Exhibit 10.**
13:49:24 **"Answer: Okay.**

13:49:25 "Question: And we were looking at Page 1231 of
13:49:28 the article.
13:49:28 "Answer: Okay.
13:49:29 "Question: And if you could go to the
13:49:31 right-hand column at the very bottom, there's the last
13:49:33 sentence. And it reads, 'Although peptides 1 and 3 have
13:49:37 been recently disclosed in a European patent application
13:49:40 describing them as bradykinin antagonists, the former was
13:49:44 discovered coincidentally and independently in our
13:49:49 laboratories.'
13:49:50 "Do you see that?
"Answer: Yes.
13:49:54 "Question: Did you insert that language into
13:49:55 this article?
13:49:57 "Answer: I don't know.
13:49:57 "Question: Why was this language inserted into
13:49:59 this article?
13:50:00 "Answer: Probably because it's, you know, it's
13:50:02 a scientific article, and it's proper to, you know,
13:50:05 reference, you know, other relevant work. You know, there's
13:50:10 other references in the paper as well. So it's probably for
13:50:13 that reason.
13:50:14 "Question: That statement says that 'The former
13:50:17 was discovered coincidentally and independently in our
13:50:21 laboratories.'

13:50:22 "Answer: Mm-hmm.

13:50:23 "Question: And is that referring to peptide one?

13:50:27 "Answer: That's how I would interpret it, yes.

13:50:28 "Question: Is it your view that peptides 1 and 3 were designed by Nova based upon Nova's earlier work that you talked about, about the beta turns and the NMR data and the sequence were designed by Nova?

13:50:30 "Answer: Yes. And that -- that's sort of what's written. I was just reading on a little bit. You know, that's how, that's how they're described, you know, each one is, you know, considered likely to stabilize the beta turn structure, so, yes.

13:50:36 "Question: Right. I have the understanding that there's a general view based upon your early work that you need conformational constraints there. And my question was now: There were specific amino acids put in Position 7 and 8, and I'm asking how does one -- how did Nova get to those specific amino acids?

13:50:42 "Answer: I don't really recall that specifically, you know. But in, but in general terms, you know, we were -- and I don't remember a lot of the specific examples, but we were -- you know, we had a strategy to make conformationally constrained peptides which incorporated

13:50:45

13:50:47

13:50:50

13:50:53

13:50:56

13:51:03

13:51:07

13:51:11

13:51:14

13:51:18

13:51:21

13:51:24

13:51:25

13:51:28

13:51:32

13:51:41

13:51:46 conformationally constrained amino acids.

13:51:49 "So these were, these were amino acids that fit
13:51:52 the category. There were probably others, you know, not
13:51:56 these, that, you know, played a similar role, not the
13:51:59 subject matter of this publication, that were tried. Some
13:52:02 of them probably had a similar effect with pharmacological
13:52:07 activity. Some of them probably didn't, you know, that's
13:52:10 part of the process of design, you know, put something in
13:52:13 there and see, see if it works properly.

13:52:15 "So also -- I mean, specifically for the, for
13:52:18 the test for tetrahydro-isoquinoline amino acid, you know,
13:52:30 again, sort of following on from NPC567, at the Position 7
13:52:35 and 8, those are phenylalanine residues. And, you know,
13:52:41 the -- you know, the -- it's a very short step to go from a
13:52:45 phenylalanine to a Tic as a very close structural mimetic
13:52:50 with all the same side chain characteristics but less
13:52:57 flexibility in the backbone and in the side chain.

13:53:00 "So I don't remember all of the different things
13:53:03 that we tried at Position 7 and 8, but those could be, you
13:53:06 know, some of the guiding principles when we were looking at
13:53:09 what we put in there.

13:53:11 "Question: Dr. Kyle, we're going to mark
13:53:13 as Kyle Exhibit 11 European patent application 89121498.3.

13:53:20 "(Kyle Exhibit 11, European patent application
13:53:25 89121498.3, marked for identification.)

13:53:36 "Question: And, Dr. Kyle, if you would just
13:53:38 take a look at that, what we've marked as Kyle Exhibit 11,
13:53:41 and let me know if you recognize the document.
13:53:43 "Answer: I don't, I don't really recog -- I
13:53:47 mean, I recognize it as a patent application, I guess, just
13:53:51 because of its content. But if I've seen it before, it's
13:53:55 been a really, really long time, so...
13:54:05 "Question: If you would take a look at footnote
13:54:08 17 in what's Kyle Exhibit 10.
13:54:10 "Answer: Okay.
13:54:11 "Question. And is this, what we've marked as
13:54:14 Exhibit 11, the European patent application that is being
13:54:18 cited in Footnote 10 in Kyle -- Footnote 17, excuse me, in
13:54:23 Kyle Exhibit 10?
13:54:26 "Answer: It looks like it is, yes.
13:54:32 Wait a minute. Why is the date -- wait a
13:54:36 minute. I'm not quite sure how to read the cover of this.
13:54:40 It looks like the date in my reference -- I mean, the
13:54:43 number 891 and so forth is the same. That date is 1990,
13:54:51 but then there's a stamp on this of 1989. Is that, is that
13:54:54 unrelated to the, to the document, or is there another date
13:54:59 on this?
13:55:00 "Question: Well, Dr. Kyle, I was going to
13:55:02 actually ask you why it was -- the date on Footnote 17 was
13:55:07 1990 when if you look at the date of the cover of Exhibit

13:55:10 **11, it says, 'Date of receipt,' and there's '21.11.1989.'**

13:55:28 **"Answer: Yeah. I don't know.**

13:55:30 **"Question: If on Exhibit 11, if you could turn to Page 29.**

13:55:33 **"Answer: 29. Okay.**

13:55:34 **"Question: And at the top of 29, there is what looks to be Example 24, and there's a peptide sequence.**

13:55:35 **"Do you see that?**

13:55:38 **"Answer: Yes.**

13:55:43 **"Question: Is that peptide sequence the same as the peptide sequence -- the sequence of peptide three on Page 1231 of Kyle Exhibit 10?**

13:55:45 **"Answer: I mean, yeah, assuming what they're calling T-h-i-a, Thi, assuming that that is thienylalanine, which is what we used for thia, assuming that's the same, then it looks like the same sequence.**

13:55:47 **"Question: Okay. Thank you.**

13:55:50 **"And if you could turn to page 33 of Kyle Exhibit 11. And if you look down almost -- well, the second example from the bottom, Exhibit 48 --**

13:56:05 **"Answer: Mm-hmm.**

13:56:07 **"Question: -- is that sequence the same as peptide one in Kyle Exhibit 10?**

13:56:16 **"Answer: Yeah, it looks the same.**

13:56:25 **"Question: We're going to mark as Kyle Exhibit**

13:56:32

13:56:33

13:56:35

13:56:39

13:56:42

13:56:44

13:56:46

13:56:50

13:56:52

13:56:55 12 the European patent application publication 370453.

13:57:27 "(Kyle Exhibit 12, European patent application

13:57:31 publication 0370453, marked for identification.

13:57:38 "Question: And, Dr. Kyle, if you could take a

13:57:41 look at Exhibit 12 and let me know if you recognize that

13:57:43 document.

13:57:44 "Answer: I mean, I recognize it as a European

13:57:47 patent application or issue patent. I'm not sure. But,

13:57:50 yes, I recognize it as that.

13:57:55 "Question: And if you'd look at the front

13:58:03 cover of Exhibit 12 and also the front cover of Exhibit 11.

13:58:06 "Answer: Mm-hmm.

13:58:07 "Question: On Exhibit 11 do you see where it

13:58:12 says, 'Application number,' and then it has '89121498.3'?

"Answer: Yes.

13:58:31 "Question: And then if you would look at

13:58:33 Exhibit 12, and there is -- for entry number 21 at the top

13:58:37 there is the No. 89121498.3.

13:58:43 "Do you see that?

13:58:44 "Answer: Yes.

13:58:47 "Question: And if you would take a look at

13:58:52 Exhibit 11. Do you see the date of receipt is 21.11.1989?

13:59:00 It's the stamp.

13:59:01 "Answer: Yes, I see it. Yes.

13:59:03 "Question: And if you would take a look at

13:59:07 **Exhibit 12, and do you see that entry number 22 at the top**
13:59:11 **is 21.11.89?**
13:59:16 **"Answer: Yes, I see it.**
13:59:17 **"Question: And do you see the entry for No. 43**
13:59:20 **on Exhibit 12 has the date of 30.05.90?**
13:59:36 **"Answer: Yes, I see it, 30.05.90, yes. Why is,**
13:59:44 **what is that?**
13:59:59 **"Question: That is the date of publication of**
14:00:02 **registration.**
14:00:02 **"Answer: Oh, okay. Yeah, I see it.**
14:00:05 **"Question: So I will represent to you that that**
14:00:08 **is the date of the publication, which is Exhibit 12, of the**
14:00:14 **application that is in Exhibit 11.**
14:00:17 **"Answer: Oh, okay.**
14:02:40 **"Question: So, Dr. Kyle, if you would turn to**
14:03:28 **Page 14 of Exhibit 12. And do you see Example 24, about**
14:03:34 **the --**
14:03:36 **"Answer: Did you say Page -- sorry. Did you**
14:03:40 **say Page 12?**
14:03:54 **"Question: Page 14?**
14:03:56 **"Answer: Oh, 14. Oh, yes. Example 24. Sorry.**
14:04:03 **I was looking at the -- I think they're the other numbers.**
14:04:08 **"Question: Oh, that's okay.**
14:04:10 **"Answer: Okay. Yeah, I see it. 24.**
14:04:13 **"Question: Is that the same amino acid sequence**

14:04:15 **that is peptide 3 in Kyle Exhibit 10?**

14:04:21 **"Answer: Yes, looks the same.**

14:04:26 **"Question: If you would turn to Page 17 of Kyle Exhibit 12. And if you would look at exhibit -- excuse me -- Example 48, and is that amino acid sequence the same as the amino acid sequence in Kyle Exhibit 10 for peptide 1 at Figure 1?**

14:05:07 **"Answer: Looks the same, yes.**

14:05:10 **"Question: So isn't it the case that the peptide 1 and peptide 3 that were reported in Kyle Exhibit 10 were already in a published patent application which is Exhibit 12, on May 30th of 1990?**

14:05:35 **"Answer: Would you just say that one more time? Isn't it the case what?**

14:05:41 **"Question: Sure. Isn't it the case that the peptide 1 and peptide 3 --**

14:05:47 **"Answer: Uh-huh.**

14:05:48 **"Question: -- that were reported in Kyle Exhibit 10 --**

14:05:52 **"Answer: Uh-huh.**

14:05:53 **"Question: -- were already in a published patent application, which is Exhibit 12, on May 30th of 1990?**

14:06:00 **"Answer: Yes, looks that way.**

14:06:03 **"Question: When you submitted this manuscript**

14:06:09 at Kyle Exhibit 10, were you aware of what was disclosed in
14:06:18 Exhibit 12?
14:06:22 "Answer: I don't have a clear memory of that, I
14:06:28 don't believe so.
14:06:38 "Question: And you don't have a recollection of
14:06:41 who inserted the language in Kyle Exhibit 10 that refers to
14:06:46 the European patent application that's referenced at
14:06:50 Footnote 17?
14:06:52 "Answer: I do not have a clear, a clear memory
14:06:55 of that, no.
14:06:56 "Question: Do you have any memory of it at all?
14:07:03 "Answer: Not really. Like what -- you why is
14:07:06 it, why is it there? Not really.
14:07:11 "Question: And is it your view that, still that
14:07:15 peptides 1 through 5 were developed in your laboratory based
14:07:26 upon the earlier conformationally constrained data that you
14:07:33 had generated?
14:07:35 "Answer: Yes. That was the purpose, that was
14:07:38 the -- that was our strategy, and these are some of our
14:07:44 peptides.
14:07:45 "Ms. Kuzmich: I'm going to have you mark as
14:07:48 Kyle Exhibit 13 a letter dated March 25, 1991, from an S.J.
14:07:59 Enna, Ph.D., to a Dr. Wingefeld.
14:08:05 "And, Dr. Kyle, if you could take a moment and
14:08:14 let me know if you recognize Exhibit 13.

14:08:18 "Answer: Yes, I recognize it as a memorandum
14:08:21 from Nova. I recognize that it's from Sam Enna, who is, you
14:08:28 know, the vice president of research from the time. I don't
14:08:32 have any specific recollection of the memo from when I was
14:08:38 there. I see that I'm cc'd on it. I recognize all the
14:08:42 names on the cc list. So, yes, I do recognize it.
14:08:46 "Question: Do you have any recollection of
14:08:56 discussions within Nova with respect to drafting this letter
14:09:01 to Dr. Wingefeld?
14:09:05 "Answer: No recollection of that.
14:09:07 "Question: Were you involved in any of the
14:09:11 discussions, if there were any, that dealt with whether a
14:09:17 letter to Dr. Wingefeld should be sent with an apology for
14:09:23 failing to cite the original disclosure by Hoechst?
14:09:28 "Mr. Stull: Objection to form.
14:09:32 "Answer: No, I don't remember that.
14:09:34 "Question: The last sentence on the first full
14:09:38 paragraph states, 'Like you, I trust this incident will not
14:09:44 affect our relationship.'
14:09:48 "Do you see that?
14:09:49 "Answer: I do, yes.
14:09:50 "Question: Do you have any understanding of
14:09:51 what relationship Dr. Enna was referring to?
14:09:55 "Answer: No. I'm reading, I'm reading that
14:09:59 right now and I'm sort of surprised and wondering because I

14:10:04 **have no recollection of a relationship with them in the**
14:10:08 **bradykinin space, at my level. I have no recollection of**
14:10:11 **that. So I really don't know what relationship. Maybe it's**
14:10:15 **a personal relationship. I'm not sure.**
14:10:18 **"Question: Is the structure of the bradykinin**
14:10:26 **analog that is identified in Kyle Exhibit 13, is that**
14:10:34 **peptide 1 of -- in Figure 1 of Kyle Exhibit 10?**
14:10:41 **"Answer: Yes.**
14:10:47 **"Question: As you sit here today, you have no**
14:10:50 **recollection of a relationship in the bradykinin antagonist**
14:10:55 **space between Nova and Hoechst; is that correct?**
14:10:58 **"Answer: Yeah, no recollection of that.**
14:11:00 **"Question: Dr. Kyle, I'm going to have the**
14:11:03 **court reporter mark as Kyle Exhibit 16 a U.S. Patent No.**
14:11:13 **6,288,036.**
14:11:18 **"And, Dr. Kyle, if you would just take a moment**
14:11:26 **to take a look at what we've marked as Exhibit 16 and let me**
14:11:31 **know if you recognize this document.**
14:11:33 **"Answer: I do recognize it.**
14:11:35 **"Question: And what is the document?**
14:11:37 **"Answer: I mean, I recognize it as an issued**
14:11:41 **U.S. patent for bradykinin peptides where I'm one of the**
14:11:46 **inventors.**
14:11:46 **"Question: Dr. Kyle, if you could turn to the**
14:11:50 **last page of Exhibit 16.**

14:11:56 "Answer: Okay.

14:11:56 "Question: And in Column 36 at Line 14 begins 'Claim 14.' Do you see that?

14:12:04 "Answer: Yes.

14:12:09 "Question: And the first structure identified in Claim 14 is a structure that has D-Tic at Position 7 and the hydroxy proline ether at Position 8; is that correct?

14:12:15 "Answer: Yes.

14:12:23 "Question: If you could turn also to now Page 10 of Exhibit 12, Dr. Kyle.

14:12:31 "Answer: 10 of Exhibit 12. Okay.

14:12:39 "Question: And if you would take a look, there's a table.

14:12:43 "Answer: Uh-huh.

14:12:45 "Question: And at Line 24, on the colored Line 24 there's a peptide. It's a bit hard to get the lines together sometimes with the structure, so I'll read out the structure. "It's H-(D-Arg)-Arg-Pro-Hyp-Gly-Thia-Ser-(D)-Tic-Aoc-Arg-OH.

14:12:49 "Do you see that?

14:12:56 "Answer: Yes.

14:12:58 "Question: And what is the difference between that peptide sequence and the peptide sequence at Claim 14 of your '036 patent, which is marked as Exhibit 16.

14:13:04 "Answer: You're asking me what is the

14:13:09

14:13:13

14:13:26

14:13:28

14:13:29

14:13:29

14:13:32

14:13:39

14:13:46

14:13:47 difference between the two peptides?
14:13:50 "Question: Yes.
14:13:55 "So what is the significant difference, if any,
14:13:58 between Compound -- the first compound listed in Claim 14 of
14:14:03 Exhibit 16 and the compound that we read into the record
14:14:11 that's at Line 24 of Exhibit 12, if we assume that the
14:14:18 hydroxyproline at amino acid 3 is four hydroxyproline?
14:14:26 "Answer: Sorry. My head is spinning a little
14:14:29 bit on the Line 15 of Page 14 and all that. So could I just
14:14:35 sort of clarify?
14:14:37 "Question: Sure.
14:14:38 "Answer: You're asking me what is the
14:14:39 difference between the Aoc and the transmethyl ether of
14:14:44 hydroxy proline?
14:14:46 "Question: Well, if those are the only
14:14:48 differences.
14:14:49 "Answer: Yeah.
14:14:49 "Question: That's the only difference between
14:14:51 what you see in Compound 1 of Claim 14?
14:14:54 "Answer: Yeah.
14:14:54 "Question: And the amino acid sequence at Line
14:15:02 24 of Exhibit 12, is there any significant difference
14:15:06 between the two molecules?
14:15:08 "Answer: Well, they're different, they're
14:15:11 different molecules. They're different because they're

14:15:15 different. You know, a different number of atoms, different
14:15:19 size. The stereochemistry is different.
14:15:23 "For example, if you look at the -- okay,
14:15:26 sorry -- in Document 10, Kyle 164 --
14:15:33 "Question: Yeah, yeah.
14:15:34 "Answer: -- if you look at the top right corner
14:15:37 of, like, of 3A, for example, that structure 3A.
14:15:43 "Question: One minute.
14:15:45 "Answer: It's this, this one.
14:15:47 "Question: Got it.
14:15:49 "Answer: Yeah. So if you look at the
14:16:00 structure, so the stereochemistry, if you'll notice that the
14:16:09 bridgehead carbons of the two fused five numbered rings,
14:16:16 there is a dot. That just means that it's a cis, it's a cis
14:16:19 geometry. The hydroxyproline ether, even though it is a
14:16:25 completely different molecule, but still if you tried to
14:16:27 make a similarity, it's a transgeometry, so it's opposite
14:16:32 geometric isomer. That's one difference.
14:16:35 There is no, there's no oxygen in the Aoc
14:16:41 molecule. There is no heteroatom, in the hydroxyproline
14:16:46 ether there is an oxygen heteroatom. So that is a different
14:16:51 size and a different electrostatic than would be, like, in a
14:16:57 carboxylic like Aoc, you know. And then the hydroxyproline
14:17:03 ether, in this example, is the transmethyl ether. That's
14:17:09 one carbon. There are more carbons in the Aoc residue. So

14:17:17 sort of at the atomic scale there is differences between the
14:17:20 two, and those would be some of the key differences.
14:17:23 "Question: Is there anything that you can
14:17:29 recall that Hoechst was doing through their patent
14:17:36 application process that impacted Nova's research in
14:17:42 bradykinin antagonists in any way?
14:17:44 "Answer: I don't think I would have any way to
14:17:47 know anything about their patent application process."
14:17:55 MR. HAUG: Thank you, Your Honor.
14:17:58 Plaintiffs will next call Dr. Bell, Dr. Gregory
14:18:02 Bell. Mr. Blumenfeld will conduct the examination.
14:18:17 MR. WIESEN: Your Honor, if I may, Mr. Sherry
14:18:19 from my office will be conducting the cross-examination. So
14:18:22 we are going to switch seats to put him in the right spot.
14:18:26 THE COURT: Mr. Blumenfeld, do you have some
14:18:28 binders?
14:18:29 MR. BLUMENFELD: I do.
14:18:30 ... GREGORY KNOX BELL, having been duly sworn as
14:18:36 a witness, was examined and testified as follows ...
14:18:48 THE COURT: Good afternoon, Doctor.
14:18:51 THE WITNESS: Good afternoon.
14:18:53 THE COURT: Doctor, I will caution you, when you
14:18:54 step down from that stand, be careful of that step. Not
14:18:59 much space there.
14:19:19 DIRECT EXAMINATION

14:19:20 **BY MR. BLUMENFELD:**

14:19:33 Q. **Good afternoon, Dr. Bell.**

14:19:34 A. **Good afternoon.**

14:19:35 Q. **Can you tell us where you work?**

14:19:41 A. **Oh, I am a group vice president at Charles River Associates. It's a global economics and management consulting firm.**

14:19:48 Q. **And are you an economist?**

14:19:51 A. **I am, yes.**

14:19:51 Q. **What do you do at Charles River Associates?**

14:19:56 A. **I have certain admin responsibilities. I lead the global life sciences practice. In that context, I work on strategy assignments, launching products in the pharmaceutical industry and the like, and work in expert witness litigation settings.**

14:20:18 Q. **Can you give us just a little bigger view of what Charles River Associates does, what types of things they do?**

14:20:25 A. **Well, as a consulting firm on the strategy side, for instance, we would help companies launch products. I have launched probably 30 pharmaceuticals. The practice has launched maybe close to 80 now. Working with physicians to decide or to determine how they make prescribing decisions, with payors on how they make decisions on which products to cover on their formularies and the like. With patients on their willingness to pay, how they use the products. So**

14:21:03 it's a fairly broad set of commercialization strategy
14:21:07 consulting work.
14:21:09 On the expert witness side, I testify in a
14:21:14 variety of different venues on a wide variety of issues
14:21:19 related to economics, damages, valuation, that sort of
14:21:22 thing.
14:21:22 Q. How long have you been at Charles River Associates?
14:21:26 A. 25 years.
14:21:26 Q. And can you just briefly go through your educational
14:21:31 background prior to the 25 years?
14:21:34 A. Sure. So I have a Bachelor's degree in business
14:21:43 administration, a minor in economics, with highest honors
14:21:47 from Simon Fraser University. That's in British Columbia,
14:21:52 Canada. I have a Master's in business administration from
14:21:55 Harvard University, also with highest honors. And I have a
14:21:59 Ph.D. in business economics, also from Harvard University.
14:22:02 Q. And have you testified as an expert witness before?
14:22:07 A. I have.
14:22:07 Q. Do you have in front of you your CV? I think it's
14:22:15 PTX-80 in your notebook.
14:22:19 A. Yes.
14:22:19 Q. And does that set forth your educational and
14:22:24 professional background?
14:22:25 A. It does, yes.
14:22:28 MR. BLUMENFELD: Your Honor, we offer Dr. Bell

14:22:30 as an expert in economics and strategy in the life sciences
14:22:36 industry.
14:22:38 MR. SHERRY: No objection.
14:22:38 THE COURT: The doctor is accepted as an expert
14:22:40 in those fields.
14:22:42 MR. BLUMENFELD: Thank you, Your Honor.
14:22:42 BY MR. BLUMENFELD:
14:22:43 Q. Have you prepared some slides to help you with your
14:22:45 testimony today?
14:22:46 A. I have.
14:22:29 Q. And can you tell us -- put up the first slide, which
14:22:45 is 4.1. Can you tell us briefly what issues you looked at
14:22:48 and what opinions you've reached?
14:22:51 A. So I'm looking at the issue of whether or not Firazyr
14:22:55 is a commercial success. In that context, assessing whether
14:23:01 or not there was a market opportunity for the product, in
14:23:05 that respect, looking at sales, growth of sales,
14:23:09 profitability in terms of profits made by Shire, sales in
14:23:15 comparison to other products that have been indicated for
14:23:18 the treatment of acute attacks of HAE, and then the extent
14:23:25 to which that market opportunity has a nexus with or is due
14:23:29 to the patented invention, which I understand to be the
14:23:34 icatibant molecule.
14:23:34 Q. And have you reached an opinion as to whether Firazyr
14:23:38 is a commercial success?

14:23:38 A. **I have, and I have concluded that it is with respect**
14:23:43 **to both the market opportunity and the nexus.**
14:23:45 Q. **Let's talk about some of those issues, and let's start**
14:23:52 **with the first one that's sales. What sales data did you**
14:23:56 **look at?**
14:23:57 A. **The sales data from Shire's books and records.**
14:24:00 Q. **And did you look at sales data for Firazyr and for**
14:24:06 **other products?**
14:24:08 A. **I did. Books and records of Shire just addressed**
14:24:12 **Firazyr. In that respect, I was looking at sales in dollars**
14:24:16 **and sales in units.**
14:24:16 Q. **Okay. Let's look at Demonstrative Exhibit 4, the next**
14:24:25 **one, 4.3.**
14:24:28 **And can you tell us what is shown on 4.3?**
14:24:31 A. **So this is showing a graph of the net sales, net of**
14:24:36 **any discounts, et cetera, realized by Shire in the U.S. So**
14:24:42 **2011 was the first year, so the product was on the market**
14:24:47 **for about four months. Came on in August. The first full**
14:24:52 **year of sales about 90 million, and that has grown to $511**
14:24:56 **million in sales by 2016. So that was about a 50 percent**
14:25:03 **per year growth rate year on year.**
14:25:06 **And then the green line there is showing**
14:25:08 **the syringes sold. So it is sold as a syringe. And through**
14:25:13 **2015, up to 48,000 syringes, and then through, I think I**
14:25:19 **have data to November of 2016, I think that's up to around**

14:25:25 **52,000 syringes.**

14:25:28 **The other point I guess I would just draw**
14:25:30 **attention to on this graph, you sort of see that the dollar**
14:25:34 **sales are going up faster than the unit sales, and that**
14:25:40 **basically is indicating that sales are growing as the price**
14:25:45 **is increasing, and that's clearly feeding into my opinion**
14:25:49 **regarding the obvious existence of a significant market**
14:25:53 **opportunity for this product.**
14:25:55 Q. **And the data that you used on PDX-4.3, is that in**
14:26:02 **PTX-81, 82, 143 and 144 that are listed at the bottom?**
14:26:07 A. **Yes, that's correct.**
14:26:08 Q. **And are those all in your notebook?**
14:26:10 A. **Yes, they are.**
14:26:11 Q. **Now, when you have looked at this data, what does it**
14:26:19 **tell you about the commercial success of the Firazyr**
14:26:23 **product?**
14:26:23 A. **Well, again, as I indicated, you know, sales have**
14:26:28 **grown in excess of half a billion after five years on the**
14:26:35 **market, five full years on the market. Those sales have**
14:26:39 **grown as the price has increased.**
14:26:42 **There clearly is a significant demand for**
14:26:45 **this product in U.S. market, and that is this point about,**
14:26:50 **you know, the first half of commercial success is, is there**
14:26:54 **market opportunity for the product.**
14:26:56 Q. **Now, in addition to actual sales, did you consider**

14:27:01 sales expectations?
14:27:02 A. Yes. That was another thing I looked at, sure.
14:27:05 Q. And did you look at Shire's expectations in the
14:27:11 market?
14:27:11 A. Yes. There were sort of two sets of Shire
14:27:14 expectations. They had expectations at launch and then you
14:27:17 got the year on year budget.
14:27:18 Q. Let's put up the next demonstrative, 4.4. And can you
14:27:25 tell us what is shown on Exhibit 4.4?
14:27:27 A. Well, 4.4, that's the pale blue bars, those are the
14:27:35 budgeted sales, so the expectation each year developed by
14:27:42 Shire, and that's, as you can imagine, updated each year.
14:27:46 So the 2012 budget expectation is set in 2011. The 2013 set
14:27:52 in 2012, et cetera.
14:27:53 And what you see is the dark blue bar is
14:27:57 the actual sales, and then each year but for 2015, actual
14:28:01 sales have outperformed even Shire's continually updated
14:28:08 expectations. Again, indicating the, supporting the idea of
14:28:14 the market opportunity for the product.
14:28:17 The expectations that Shire set just prior to
14:28:20 launch, I think if I recall correctly, had 2016 sales that
14:28:26 were, you know, well less than 300 million, and in
14:28:30 comparison, you know, we've got actual sales greater than
14:28:33 500 million. And that's, again, just the U.S.
14:28:37 Q. And, again, at the bottom of slide 4.4, there's

14:28:40 **a list of exhibits, PTX-145, 146, 147, 378, 379, and 380.**
14:28:50 **And is that where you got the information for this chart?**
14:28:53 A. **Yes, that's right. Each one corresponds to a year.**
14:28:56 Q. **And are those also in your notebook?**
14:28:59 A. **They are, yes.**
14:29:00 Q. **Did you also consider the expectations versus the**
14:29:06 **performance by third parties?**
14:29:09 A. **Yes, I did.**
14:29:11 Q. **And can you turn to PTX-148.**
14:29:21 A. **Okay.**
14:29:22 Q. **And can you tell us what Exhibit 148 is?**
14:29:25 A. **Oh, well, this is the sort of standard investment**
14:29:30 **analyst report. This one is by William Blair, one of the**
14:29:34 **investment firms. It's dated October 24th, 2013.**
14:29:39 Q. **And if you look at the second paragraph, do you see**
14:29:53 **that there is a reference to Firazyr being the standout in**
14:29:59 **the human genetic therapies unit of Shire?**
14:30:03 A. **Yes, and it's making the point that the actual sales**
14:30:05 **were at the time well ahead of the William Blair estimate of**
14:30:12 **40 million in terms of expected sales, and then a consensus**
14:30:16 **of 50 million. The consensus is sort of the consensus of**
14:30:22 **all other analysts that are following Shire and reporting**
14:30:25 **expectations of Firazyr sales.**
14:30:27 Q. **And how did this affect your opinion about the**
14:30:30 **commercial success of Firazyr?**

14:30:32 A. **Well, it is simply more support for the fact that there was a market opportunity for this product and, in fact, an opportunity that exceeded expectations.**

14:30:44 Q. **Did you also consider analyses by other third parties on expectations for the sales of Firazyr?**

14:30:53 A. **Yes.**

14:30:56 Q. **And how did those affect your opinion?**

14:30:58 A. **Again, just more support for basically the same point.**

14:31:03 Q. **In addition to sales and expectations, did you also consider the profitability of Firazyr?**

14:31:13 A. **Yes.**

14:31:14 Q. **And looking at the profitability information, did you reach any conclusions?**

14:31:19 A. **I did. I mean, this is a product that has generated significant profits for Shire.**

14:31:29 Q. **Can we go back to the demonstratives? And let's put up 4.5.**

14:31:33 **And can you tell us what is shown on Demonstrative Exhibit 4.5?**

14:31:39 A. **Sure. Basically, what we're seeing here is the operating income, that's the light blue bars. On top of that is operating expenses. That's the yellow part. On top of that is cost of goods sold. That's the green part. And the total height of the bar refers to the global net sales of Firazyr.**

14:32:01

14:32:02 **So this is a global picture and Shire's**
14:32:07 **global profits. You can see in 2016, the profit return at**
14:32:15 **the bottom line for Shire due to sales of, global sales of**
14:32:19 **Firazyr, was 427 million. That was in the neighborhood of**
14:32:22 **about a 74 percent profit margin.**
14:32:26 **And over this five-year -- well, from 2011**
14:32:32 **forward, six-year time span, you know, the product has**
14:32:37 **returned $1.2 billion to Shire. That's shown on the graph**
14:32:41 **on the far right, which is just adding together the total**
14:32:46 **global sales, total global cost of sales, operating**
14:32:49 **expenses, et cetera.**
14:32:49 Q. **And this was only through 2016; is that right?**
14:32:53 A. **Oh, yes. That's correct. And, you know, obviously,**
14:32:57 **the product continues to sell in 2017 and expectations**
14:33:02 **continue to mount for 2018.**
14:33:05 Q. **And, again, if you look at the source, you have listed**
14:33:08 **PTX-87 and 143. Are those the documents showing this**
14:33:14 **information?**
14:33:15 A. **They are, yes.**
14:33:16 Q. **And are those in your notebook?**
14:33:18 A. **They are, yes.**
14:33:20 Q. **And I think you may have already answered this at**
14:33:24 **least in part, but how does this global profitability**
14:33:28 **information affect your opinion about the commercial success**
14:33:33 **of Firazyr?**

14:33:34 A. **Well, again, it's supporting the fact that there's a**
14:33:37 **clear market opportunity for the product, generating**
14:33:43 **$1.2 billion in profit.**
14:33:44 Q. **And in addition to looking at the sales and**
14:33:48 **profitability of Firazyr alone, have you analyzed Firazyr's**
14:33:54 **performance in the market relative to other treatments for**
14:33:59 **acute attacks of hereditary angioedema?**
14:34:04 A. **Yes, I have. Particularly, the indicated products,**
14:34:06 **yes.**
14:34:07 Q. **And what data did you look at?**
14:34:10 A. **Well, there's a service, one of the compilers of**
14:34:15 **information in the pharmaceutical industry called**
14:34:19 **EvaluatePharma, and they prepare reports on different**
14:34:22 **therapeutic categories, and one of their reports had to do**
14:34:27 **with treatments for HAE.**
14:34:30 Q. **Let me put up Demonstrative 4.6. And can you tell us**
14:34:36 **what is shown on 4.6?**
14:34:38 A. **Well, this is just graphing the information that was**
14:34:42 **provided by EvaluatePharma for each year that Firazyr was**
14:34:49 **available for sale in the U.S., so starting in 2011. And**
14:34:55 **then the other three products that are indicated by the FDA**
14:34:58 **for the treatment of acute attacks of HAE are Berinert,**
14:35:06 **Kalbitor and Ruconest.**
14:35:10 **You can see Berinert by 2012, Firazyr is**
14:35:14 **the lead product in the marketplace, and certainly by 2016,**

14:35:20 it's selling considerably more than the other products
14:35:24 combined.
14:35:25 Q. And, again, the source information shown is PTX-88 and
14:35:30 125. Are those in your notebook?
14:35:32 A. Yes. I'm sorry. Yes, they are.
14:35:34 Q. A couple questions about this. The Berinert data
14:35:38 looks like it starts in 2013. Why do you not have
14:35:43 information about the sales of Berinert in the U.S. before
14:35:49 2013?
14:35:50 A. Well, that wasn't reported on EvaluatePharma -- wasn't
14:35:55 reported, I'm sorry, by EvaluatePharma, and CSL Behring, we
14:36:01 could not find information where it was separately reporting
14:36:05 U.S. sales of Berinert. So it just would appear that the
14:36:09 data were not made publicly available.
14:36:12 Certainly, Berinert was on the market. I
14:36:14 think you probably heard earlier that Berinert was
14:36:17 introduced around 2008 to 2009 in the U.S.
14:36:21 Q. One other question and we heard yesterday about
14:36:24 Firazyr, Berinert and Kalbitor. The fourth product you have
14:36:29 listed there, Ruconest, I'm not sure we have heard anything
14:36:33 about that. Can you tell us what that is?
14:36:35 A. Oh. Well, that's another C1 inhibitor. It has to be
14:36:40 reconstituted and then an IV infusion, much like, much like
14:36:47 Berinert. And it was -- I believe it's currently being
14:36:51 marketed by a company called Pharming.

14:36:58 Q. **And just one more question on this, Doctor. What does**
14:37:02 **this tell you about the commercial success of Firazyr in the**
14:37:05 **market?**
14:37:07 A. **Well, again, it's pointing to the significant market**
14:37:10 **opportunity for this product. It obviously took significant**
14:37:13 **sales and share from Berinert and Kalbitor that had been**
14:37:18 **available in the U.S. market prior to the arrival of**
14:37:23 **Firazyr. And physicians are obviously continuing to**
14:37:27 **prescribe the product because it works. Patients are**
14:37:32 **continuing to use the product and payors are obviously**
14:37:37 **continuing to pay for it, all supporting this point about a**
14:37:40 **significant market opportunity.**
14:37:41 Q. **Do you have an understanding, Dr. Bell, of what the**
14:37:47 **patented invention is in this case?**
14:37:48 A. **Well, I understand that the patented invention is the**
14:37:53 **molecule icatibant.**
14:37:56 Q. **And in your opinion, is the commercial success of**
14:38:00 **Firazyr due to that molecule, icatibant?**
14:38:05 A. **I believe, I believe it is due to that based on the**
14:38:10 **work I've done and the opinions expressed by others. It is**
14:38:17 **the attributes of that icatibant molecule that make it a**
14:38:20 **safe and efficacious treatment for the acute attacks of HAE**
14:38:24 **as labeled by the FDA, and it's the attributes of the**
14:38:31 **icatibant molecule that make it self administered or able to**
14:38:34 **be self-administered and able to be self-administered**

14:38:39 **subcutaneously, i.e., by an injection.**

14:38:42 Q. **Now, have you had an opportunity --**

14:38:44 **THE COURT: Hold on a second.**

14:38:45 **Yes?**

14:38:46 **MR. SHERRY: Objection to the last question. It's a little beyond the scope of the economist.**

14:38:50 **THE COURT: Beyond the scope of what?**

14:38:52 **MR. SHERRY: His expertise as an economist.**

14:38:54 **THE COURT: I don't remember the question, quite frankly. What was the question?**

14:38:57 **MR. BLUMENFELD: The question was whether in his opinion, the commercial success was due to the icatibant. I don't think that's beyond the economist's --**

14:39:07 **MR. SHERRY: It was the testimony that the molecule itself was responsible for the features that were responsible for the success.**

14:39:15 **THE COURT: Doesn't he likely rely on the opinions of others?**

14:39:20 **MR. BLUMENFELD: We're about to get to that, Your Honor.**

14:39:22 **MR. SHERRY: That's fine.**

14:39:23 **BY MR. BLUMENFELD:**

14:39:24 Q. **Dr. Bell, have you had the opportunity to review Dr. Kaplan's testimony from yesterday?**

14:39:25 A. **I have, yes.**

14:39:30

14:39:32

14:39:33 Q. **And yesterday he put up this chart, which is PDX-4.7.**
14:39:40 **Have you had an opportunity to review this?**
14:39:43 A. **Yes.**
14:40:00 Q. **And did you consider Dr. Kaplan's testimony and this**
14:40:08 **chart in forming your opinion that the commercial success of**
14:40:14 **Firazyr was due to the icatibant?**
14:40:18 A. **Well, yes. Again, my understanding, you know, it is**
14:40:23 **the attributes of that icatibant molecule that make it a**
14:40:28 **safe and effective treatment for acute attacks of HAE. The**
14:40:35 **no anaphylaxis is a reference to the immunogenicity.**
14:40:42 **Kalbitor, one of those other treatments, has that black box**
14:40:46 **warning and actually must be administered under the**
14:40:49 **supervision of a health care professional, partly for that**
14:40:52 **reason.**
14:40:53 **No systemic side effects. Again, that means**
14:40:55 **that it is a product that patients can use for themselves,**
14:41:00 **by themselves, without the direction of a medical**
14:41:05 **professional, once, you know, they are taught how to inject.**
14:41:09 **The dosage form, again, it is a property of the**
14:41:12 **molecule, as I understand it, that enables it to be packaged**
14:41:16 **in a prefilled syringe. You don't have to refrigerate it.**
14:41:19 **So it's something that the patient can have near them.**
14:41:24 **One of the things that Dr. Kaplan was talking**
14:41:26 **about, and it has been in other information, is that the**
14:41:31 **sooner one is able to treat one of these acute attacks, the**

14:41:34 1 **better off the patient is going to be.**
14:41:37 2 **So this is a product that, once the patient**
14:41:41 3 **feels an attack coming on, is hopefully within arm's reach**
14:41:48 4 **and they are able to use it, as opposed to potentially**
14:41:51 5 **having to go see a medical professional for Kalbitor or**
14:41:54 6 **having to set up an infusion apparatus and sort of**
14:41:58 7 **reconstitute the stuff, which is the case for Berinert and**
14:42:06 8 **Ruconest.**
14:42:06 9 **That leads to that third sort of set of bullets**
14:42:10 10 **there on administration. It is a subcutaneous injection.**
14:42:13 11 **You don't have to find the vein, stick yourself.**
14:42:17 12 **And again, you can do it on your own. And since**
14:42:21 13 **these attacks, as I understand it, you know, you can't**
14:42:26 14 **predict when they are going to come, you don't know how**
14:42:28 15 **severe they are going to be, you don't know exactly where**
14:42:31 16 **they might afflict the patient, having a product that the**
14:42:39 17 **patient is able to make the decision to use and use quickly,**
14:42:45 18 **given that addressing these attacks quickly is important,**
14:42:50 19 **goes directly to this whole issue of why this product,**
14:42:55 20 **Firazyr, is such a success in the marketplace.**
14:42:57 21 **It is that nexus to the attributes of the**
14:43:01 22 **molecule.**
14:43:03 23 **THE COURT: Counsel, what is your name again?**
14:43:05 24 **MR. SHERRY: Mr. Sherry.**
14:43:07 25 **THE COURT: You should get Mr. Wiesen to take**

14:43:10 you to dinner for instigating that objection. That's all
14:43:14 right.
14:43:15 BY MR. BLUMENFELD:
14:43:15 Q. Dr. Bell, on these last two points, the subcutaneous
14:43:19 injection and self-administration, have you seen information
14:43:36 with regard to the product?
14:43:37 A. Well, sure. There is a fair amount of market research
14:43:41 that is done every year on market studies that reflects the
14:43:47 information on physicians and patients, the physicians who
14:43:48 are prescribing these products and patients who are using
14:43:51 these products.
14:43:52 Q. Can you turn to PTX-155 in your book. Can you tell us
14:44:07 what PTX-155 is?
14:44:09 A. This is another one of these investment analyst
14:44:12 reports. This one is dated December 2010. So it is prior
14:44:16 to the launch of Firazyr and the FDA approval of Firazyr for
14:44:22 the U.S. marketplace.
14:44:22 Q. And the analysts here is someone called Evolution?
14:44:27 A. Evolution Securities.
14:44:28 Q. And the title of this is Firazyr - Under-appreciated
14:44:31 Product Opportunity.
14:44:32 Do you see that?
14:44:33 A. I do, yes.
14:44:34 Q. Can you turn to Page 5, to 155.5. Did you review the
14:44:43 data on this page and the next page?

14:44:46 A. **I did, yes, sure.**

14:44:47 Q. **And if you could just go through a little of this. Let's start with the title of this page. Can we highlight the title.**

14:44:59 **It says Firazyr - Treatment - Paradigm Shift. What did that mean to you?**

14:45:04 A. **Well, it is, again, the expectation that this is going to be self admin, subcu, available to be with the patient, that indicates a paradigm shift. You don't have to get to a medical professional. At this time, well, Ruconest wasn't in the market but Berinert and Kalbitor actually were both under the supervision of a medical professional for administration.**

14:45:34 Q. **And if you go down farther on the first page, is there a discussion of the importance of self-administration?**

14:45:42 A. **Well, yes. It's one of these three aspects that these market analysts are calling out as what sets Firazyr apart from the competition, which at that time in the U.S., for those products indicated, for the treatment of acute attacks of HAE, were Berinert and Kalbitor.**

14:46:05 Q. **Can you go down a little farther under Self-Administration, what did Evolution say in 2010 about self-administration?**

14:46:13 A. **Well, I will just quote: "We mark the ability to self-administer a room temperature, stable, pre-filled**

14:46:25 **syringe upon initiation of an attack as the most significant**
14:46:29 **differentiating factor for Firazyr versus its competition."**
14:46:35 **That is again getting at this point that the**
14:46:38 **product is available for the patient when needed. No**
14:46:42 **special prep or refrigeration or anything like that is**
14:46:47 **required.**
14:46:47 Q. **Can you turn to the next page, please. Can you**
14:46:58 **highlight the second paragraph at the top.**
14:47:01 **What does that say about self-administration?**
14:47:03 A. **Well, this is that point that I was making. "The**
14:47:08 **whole point of the addition of the 'self-administration'**
14:47:13 **indication to the label is that an HAE sufferer will be able**
14:47:17 **to keep the syringe in their handbag, or backpack, and use**
14:47:21 **it when they feel an attack coming on, rather than to have**
14:47:25 **to drive to the hospital and request a medical professional**
14:47:28 **to infuse the product.**
14:47:33 **Again, this goes back to this issue of the**
14:47:36 **sooner one is able to address one of these attacks, as I**
14:47:39 **understand it, the more -- the better that is going to be**
14:47:43 **for the patient.**
14:47:44 Q. **And can you go down to the heading in the middle of**
14:47:47 **the page called Convenience.**
14:47:52 **What did Evolution say about the convenience of**
14:47:54 **the product?**
14:47:55 A. **Well, it's echoing some of the same advantages again,**

14:48:00 it's the fact that the patients can easily carry Firazyr
14:48:03 with them -- I am quoting -- and therefore, they will be
14:48:08 well prepared to deal with an attack, because again, these
14:48:11 attacks come on, there is no obvious triggers, as I
14:48:15 understand it.
14:48:17 Q. And, finally, right at the bottom of the page, what is
14:48:22 the third heading?
14:48:24 A. Well, that's efficacy and side effects. And, of
14:48:28 course, you know, a product must be efficacious and safe in
14:48:35 order to have the opportunity to get on the market at all.
14:48:40 And they are simply commenting on the fact that the product
14:48:45 is likely to be shown to be as efficacious, at least
14:48:49 equivalent efficacy to its competitors is the quote, and
14:48:54 have an advantage in terms of safety, which is related to
14:48:59 this immunogenicity issue as I understand it.
14:49:02 Q. Dr. Bell, how did that affect your opinion on the
14:49:10 things that made Firazyr successful?
14:49:12 A. Again, it simply supports the nexus point. These are
14:49:16 the various attributes of the icatibant molecule that I have
14:49:21 identified.
14:49:22 Q. Can we next turn to JTX-13. It's also in your
14:49:28 notebook. I think it's the first document in your notebook?
14:49:31 A. Okay.
14:49:31 Q. Can you tell us what JTX-13 is?
14:49:34 A. This is another investment analyst report. This one

14:49:38 **is Cowen and Company. It's actually dated August 25, 2011,**
14:49:43 **pretty much coincident with the announcement of the FDA's**
14:49:48 **approval for the product and its launch in the U.S.**
14:49:51 **marketplace.**
14:49:51 Q. **Can we highlight the first paragraph.**
14:49:56 **What did Cowen have to say about Firazyr at the**
14:49:59 **time it was launched?**
14:50:00 A. **Well, they are talking about the important aspect that**
14:50:04 **the FDA has allowed for the inclusion of self-administration**
14:50:08 **in the label. And then they have underlined that, "This is**
14:50:12 **critical to the commercial success, as our consultants have**
14:50:16 **previously referred to self-administration as the 'holy**
14:50:22 **grail' for acute HAE treatment."**
14:50:24 Q. **And how does this affect your opinion on the reasons**
14:50:28 **for the commercial success of Firazyr?**
14:50:32 A. **Again, it's simply more support for the same points.**
14:50:37 **Having that product within arm's reach and desire, so that**
14:50:41 **patients are able to use it when needed.**
14:50:43 Q. **Now, Dr. Bell, are you aware that Fresenius has**
14:50:53 **suggested that the success of Firazyr is due to pricing and**
14:51:00 **marketing strategy?**
14:51:03 A. **Yes. I believe that's a broad characterization, I am**
14:51:07 **sure.**
14:51:07 Q. **Have you looked at those issues as well?**
14:51:09 A. **I have.**

14:51:09 Q. **Can we go back to the demonstratives. Thank you.**

14:51:17 **This is Demonstrative 4.8. Can you tell us what**

14:51:19 **this is?**

14:51:20 A. **So this is a plot over time of the list price for**

14:51:27 **these four products that are approved by the FDA for the**

14:51:30 **treatment of acute attacks of HAE. And it's -- what I have**

14:51:35 **done is made it a price per attack based on the labels for**

14:51:40 **each of the products in terms of how much use, how many**

14:51:44 **vials are required per attack.**

14:51:49 **For Kalbitor, it's three. For Firazyr, it's**

14:51:53 **one. For Berinert and Ruconest, they are actually**

14:51:57 **weight-based dosings. I am using the expectations of**

14:52:01 **average weights in the U.S.**

14:52:03 Q. **What does this data tell you about Firazyr's**

14:52:07 **commercial success and its relationship to the pricing of**

14:52:10 **the products?**

14:52:11 A. **Well, Firazyr does have the lowest list price per**

14:52:18 **attack. But the price differential is not dramatic or**

14:52:25 **significant from my perspective. And I don't see that,**

14:52:34 **i.e., this lower list price per attack, as being a primary**

14:52:37 **driver of the product's market opportunity.**

14:52:42 **In fact, there is suggestion out there in the**

14:52:45 **marketplace that it's actually Berinert that is the least**

14:52:50 **expensive treatment per attack.**

14:52:52 Q. **On that subject, can we turn to PTX-170.**

14:53:03 **Can you highlight the title of this in the third**
14:53:05 **paragraph, please.**
14:53:11 **Can you tell us what this is, Dr. Bell?**
14:53:14 A. **Well, this is just a report from CSL Behring, that is**
14:53:21 **the company that markets Berinert. The title was CSL**
14:53:26 **Behring Study shows Berinert is least costly on demand.**
14:53:30 **They are using "on demand" to refer to these products that**
14:53:33 **are approved by the FDA for the treatment of acute attacks**
14:53:36 **of HAE.**
14:53:38 **And in the paragraph that is highlighted, it's**
14:53:41 **making the point about looking at average utilization per**
14:53:46 **attack, rather than a labeled indication. Maybe just**
14:53:53 **showing, there, the sentence that starts, Berinert was the**
14:53:57 **least costly on demand treatment option for HAE in a typical**
14:54:02 **patient with 75 kilogram per body weight needing three vials**
14:54:07 **per treatment episode. Per attack, Berinert was estimated**
14:54:11 **to save patients 79.29 to $4,659 compared to Firazyr and**
14:54:21 **2,628 to $7,208 compared to Kalbitor.**
14:54:27 Q. **Turning to Fresenius's other point about Firazyr or**
14:54:37 **Shire's marketing practices, have you looked at the level of**
14:54:42 **aggressiveness of Shire's marketing practices?**
14:54:45 A. **Sure. Sort of looked at their spend, their -- yes.**
14:54:50 Q. **Could you put up 4.9, Demonstrative 4.9. What is**
14:54:59 **shown on Demonstrative 4.9?**
14:55:03 A. **What I am looking at here is I am comparing what I**

14:55:06 **call share of voice to sort of share of sales.**

14:55:11 **The idea is that one company's got a 50-percent**
14:55:16 **share of sales. It typically wouldn't surprise one to learn**
14:55:20 **that they have, they account for 50 percent of the**
14:55:24 **advertising in the category as an example.**

14:55:26 **And so we talk about share of voice kind of**
14:55:33 **relative to share of sales. So what you see here is the**
14:55:36 **share of voice is the blue bars, and that's based, these**
14:55:41 **data, on visits to physicians in terms of discussing the**
14:55:47 **products.**

14:55:48 **And that's the share of visits to physicians in**
14:55:52 **the blue bars. And in the green bars are the share of**
14:55:59 **sales.**

14:56:00 **And what is patently obvious is the green bars**
14:56:07 **for Firazyr far outweigh the blue bars, making it quite**
14:56:11 **clear Firazyr is in no way -- or Shire is no way, shape or**
14:56:16 **form, having a share of voice, calling on physicians more**
14:56:22 **aggressively than its share of sales would warrant.**

14:56:27 **In fact, it accounts for substantially fewer of**
14:56:31 **those calls than its share of sales would warrant.**

14:56:35 Q. **For example, if you would look at the share of voice**
14:56:38 **between Firazyr, Berinert, Kalbitor for 2013, and their**
14:56:45 **relative sales in the market, what does that tell you?**

14:56:48 A. **Well, basically, the share of voice for those three**
14:56:51 **products was about the same, but, obviously, the share of**

14:56:55 sales was massively different in favor of Firazyr.

14:57:01 So I just don't see how one is able to support a
14:57:05 conclusion that, you know, Shire was unduly aggressive in
14:57:12 terms of promoting Firazyr. And I will note, obviously, in
14:57:15 2013, which is what we were just looking at, that was before
14:57:20 Shire had acquired Cinryze and before Shire had acquired
14:57:26 Kalbitor.

14:57:26 Q. And is the source for this chart the exhibits that are
14:57:33 listed at the bottom, PTX-88, 94, 125 and 381?

14:57:39 A. That's correct, yes.

14:57:40 Q. And are those all in your notebook?

14:57:43 A. Yes.

14:57:31 Q. Now, can we put up what I think is our last slide,
14:57:36 4.10, and can you just walk through and explain in summary
14:57:44 your opinion about commercial success of Firazyr?

14:57:47 A. Yes. So I have concluded it's a commercial success
14:57:51 due to the attributes of the icatibant molecule. So from a
14:57:59 sales perspective, again, up at half a billion dollars of
14:58:03 sales in 2016 and continuing to grow, and that's just in the
14:58:07 U.S. Global profits for Shire of $1.2 billion through 2016,
14:58:14 again continuing to grow. And as indicated by that graph
14:58:20 that we saw earlier, clearly accounting for the vast
14:58:24 majority of sales of products that are indicated by the FDA
14:58:28 for acute attacks of HAE.

14:58:31 And I really do see those as being due to the

14:58:36 attributes of the product. It's the attributes of icatibant
14:58:40 that render it to be safe and efficacious for its
14:58:47 indication, treatment of acute attacks of HAE, and it's that
14:58:51 convenience issue, that arm's reach desire, that enable or
14:58:57 the attribute of icatibant enable the product to be
14:59:01 subcutaneous dosing and self-administration. It does not
14:59:05 have to be refrigerated. If the patient feels an attack
14:59:10 coming on, they can treat themselves promptly, and that's
14:59:16 simply not the case with respect to the other products.
14:59:19 MR. BLUMENFELD: Thank you, Dr. Bell.
14:59:20 THE COURT: Thank you, Mr. Blumenfeld. We'll
14:59:22 take a stretch and then have cross-examination.
14:59:24 (Short recess taken.)
15:17:48 THE COURT: All right. Please take your seats.
15:17:50 Your witness, counsel. Do you have some
15:17:53 binders?
15:17:56 MR. SHERRY: Yes.
15:18:00 (Binders handed to the Court and to the
15:18:03 witness.)
15:18:16 CROSS-EXAMINATION
15:18:17 BY MR. SHERRY:
15:18:21 Q. Good afternoon, Dr. Bell.
15:18:22 A. Good afternoon.
15:18:26 Q. Can we have PDX-4.8. This is one of the slides we
15:18:36 were looking at earlier?

15:18:37 A. **Yes.**

15:18:38 Q. **And this is a slide that you put together showing the**

15:18:40 **average list price per attack?**

15:18:43 A. **Yes.**

15:18:43 Q. **And that's for the Firazyr as well as Ruconest,**

15:18:52 **Berinert and Kalbitor?**

15:18:53 A. **Yes.**

15:18:54 Q. **These are your calculations?**

15:18:55 A. **Yes, based on the indications on the labels.**

15:18:57 Q. **Right. And over here we have thousands of dollars on**

15:19:00 **the left?**

15:19:01 A. **That's right.**

15:19:02 Q. **Is that right?**

15:19:03 A. **Correct.**

15:19:03 Q. **Is it fair to say that there's about a, you know, one**

15:19:08 **to $3,000 difference per attack between Firazyr and its**

15:19:14 **competitors, roughly?**

15:19:15 A. **I don't know so much about three, but I would buy, you**

15:19:23 **know, it's around 15 -- somewhere between 15 to 20 percent,**

15:19:28 **potentially.**

15:19:29 Q. **Right. And that's several thousand dollars?**

15:19:33 A. **Yes. Well, it's one --**

15:19:38 Q. **This is around eight; right? This is around eleven;**

15:19:45 **right?**

15:19:45 A. **Yes. Firazyr to Berinert line might be eight to maybe**

15:19:50 **nine-and-a-half. I could probably just look it up in my**
15:19:53 **report. It has got all the numbers on it.**
15:19:55 Q. **You're referring to PTX-093?**
15:20:00 A. **I have no idea. I said I could probably look it up in**
15:20:07 **my report.**
15:20:08 Q. **Well, if you turn to PTX-093, I believe that's in your**
15:20:11 **cross binder.**
15:20:12 A. **Oh, sorry. Yes.**
15:20:13 Q. **We have it on the screen, too.**
15:20:26 A. **That's right. Yes.**
15:20:27 Q. **These are the numbers behind the demonstrative we were**
15:20:30 **looking at before; is that right?**
15:20:32 A. **Correct. And you can see sort of lines 13, 14 and 15**
15:20:39 **for each year would give the list price a difference in**
15:20:45 **percentages.**
15:20:45 Q. **Right. Let's look at September 5th, 2014. And here**
15:20:53 **we have the actual list price per attack.**
15:20:58 A. **Yes.**
15:20:58 Q. **And this is the first date on which we have all four**
15:21:03 **products; is that right?**
15:21:04 A. **Represented in these data, that's correct. Yes.**
15:21:06 Q. **All right. And so you have between a $1,500**
15:21:10 **difference and a $3,000 difference between Firazyr and the**
15:21:14 **other products; right?**
15:21:16 A. **Yes.**

15:21:20 Q. **All right. And if we turn to November of 2016, 2016**
15:21:30 **was the last day we had sales in your analysis; is that**
15:21:35 **right, Dr. Bell? 2016?**
15:21:36 A. **Yes, correct.**
15:21:37 Q. **And so if we look at -- next page. Sorry. Yes.**
15:21:49 **Here. October 2016. Again, here you see about a $2,000**
15:21:58 **difference between Firazyr and Ruconest and 3,000 in between**
15:22:02 **Firazyr and Kalbitor, and I guess it's another 2,000 again**
15:22:07 **between Firazyr and Berinert; right?**
15:22:10 A. **Yes, those would be approximately correct, again,**
15:22:13 **based on list and indication.**
15:22:16 Q. **So according to your calculations, Firazyr is the**
15:22:21 **lower list price per attack than any of the accused HAE**
15:22:25 **products for the entire time it has been on the market. Is**
15:22:28 **that right?**
15:22:28 A. **I believe that's what my graph showed, yes.**
15:22:31 Q. **All right. And you also discussed in your direct a**
15:22:34 **study by CSL Behring?**
15:22:38 A. **That's correct.**
15:22:39 Q. **And that concerned the price of Berinert; right?**
15:22:42 A. **The price of Berinert, Kalbitor, and Firazyr.**
15:22:46 Q. **Right. And you were saying under that study, Berinert**
15:22:49 **was less expensive than Firazyr; is that right?**
15:22:51 A. **That's what CSL Behring was reporting, yes.**
15:22:55 Q. **And CSL Behring is the manufacturer of Berinert?**

15:22:58 A. **Sure.**

15:22:58 Q. **And it was able to show a lower price because it was calculating with three vials per attack whereas here you were calculating with four vials per attack?**

15:23:10 A. **Yes. As I indicated, I was being conservative, and the information on the CSL press release I believe was based on actual utilization, number of vials per attack. As I indicated, my calculations are based on the, on the label, and I believe I indicated in the report, Berinert might be three vials for women, four vials for men.**

15:23:40 Q. **You have four vials here because Berinert requires four vials if the patient is over 75 kilos; right?**

15:23:47 A. **I don't exactly recall. I think that's right.**

15:23:50 Q. **Yes. And average American patients are above 75 kilos. Right? That's why you picked four vials in your analysis?**

15:23:57 A. **My recollection is that's true for men and not so much true for women. Yes.**

15:24:04 Q. **If I --**

15:24:05 A. **At the median, as indicated in my footnotes to the exhibit, females would require three vials.**

15:24:15 Q. **And at the mean, they would require four?**

15:24:18 A. **As I sit here, I don't recall.**

15:24:20 Q. **If you look at the last page of this exhibit, it will say four.**

15:24:25 **Can I have the last page of this exhibit?**

15:24:32 **The mean body weight for an American female is 76.4 kilos?**

15:24:37 A. **Yes, that would be correct.**

15:24:38 Q. **And that's what you wrote in this exhibit to your report?**

15:24:40 A. **Yes.**

15:24:42 Q. **Now, you also said that the 2016 net sales of Firazyr were over $510 million; is that right?**

15:24:43 A. **Yes. I think it was 511, but, sure.**

15:24:44 Q. **And although you didn't mention it in your direct, in your report you calculated the number of patients on Firazyr in 2016; is that right?**

15:24:57 A. **Yes. That's, that's correct based on the market research I believe.**

15:24:59 Q. **And there are approximately 2300 patients on Firazyr in 2016?**

15:25:02 A. **I would have to refer to my report to recollection.**

15:25:05 Q. **May I have PTX-083. And we're looking at this number here.**

15:25:08 A. **Yes. That adds up to 22,016. I believe that to be correct, yes.**

15:25:10 Q. **There were 2,283 patients supporting those $510 million in sales; right?**

15:25:14 A. **Correct.**

15:25:15

15:25:19

15:25:21

15:25:25

15:25:35

15:25:38

15:25:44

15:25:45

15:25:50

15:25:51

15:25:53 Q. **And that's over $200,000 per patient; is that right, Dr. Bell?**

15:25:57 A. **That's about right, yes.**

15:25:57 Q. **Now, Shire holds a leadership position in the HAE market; right?**

15:26:09 A. **Well, it has three therapies as of 2016, Firazyr, Cinryze and Kalbitor, yes.**

15:26:14 Q. **And that's an industry leading portfolio; is that correct?**

15:26:16 A. **I believe it has been characterized that way, sure.**

15:26:29 Q. **Now, Shire acquired Firazyr in 2008; is that right?**

15:26:33 A. **Yes, I believe that's correct.**

15:26:33 Q. **And it acquired Cinryze at the beginning of 2014?**

15:26:37 A. **That's my understanding, yes.**

15:26:43 Q. **And it acquired Kalbitor at the beginning of 2016?**

15:26:46 A. **Sure.**

15:26:49 Q. **Today Shire controls the marketing efforts in the U.S. for all three of those drugs; right?**

15:26:50 A. **I believe that's correct.**

15:26:54 Q. **Firazyr is the leading brand in the treatment of acute attacks of HAE?**

15:26:55 A. **For those products that are so indicated, yes.**

15:26:57 Q. **And Cinryze is the leading brand for the prophylactic treatment of HAE; is that right?**

15:27:01 A. **Well, I -- I believe so at this point in time, yes.**

15:27:02

15:27:05

15:27:06

15:27:10

15:27:14

15:27:15

15:27:21 Q. **In fact, Cinryze sells even more than Firazyr; right?**

15:27:25 A. **I think so. I don't know that it's dramatically more, but I believe so.**

15:27:28 Q. **So Shire has controlled leading brands for both acute and prophylactic treatment of HAE since January of 2014; is that right?**

15:27:29 A. **I think that's a fair characterization, yes.**

15:27:33 Q. **Okay. Can I have PDX-4.5, please. This is the operating income and profits?**

15:27:38 A. **Yes.**

15:27:40 Q. **As discussed in your direct. So here the blue is the profits, right, on this graph?**

15:27:43 A. **Correct. Each year, yes.**

15:28:04 Q. **Right. So these three years, 2014 to 2016, were the years in which Shire controlled the leading brand in both acute and prophylactic treatment?**

15:28:05 A. **Sure.**

15:28:06 Q. **And over 80 percent of the profits that you considered were in those years; is that right?**

15:28:09 A. **I think that's -- I think that's correct. Of course, the profit profile is very similar to most pharmaceuticals. As they're three, four, five, six years out, that's where they tend to make their most money.**

15:28:11 Q. **Right. In this case, this is after Shire acquires the leading drugs in both sides of the HAE market; is that**

15:28:13

15:28:22

15:28:26

15:28:28

15:28:29

15:28:33

15:28:34

15:28:41

15:28:48

15:28:52

15:28:55

15:28:57

15:29:01 **right?**

15:29:01 A. **Well, sure, but, of course, also significant profits in 2013 and sales.**

15:29:03

15:29:05 Q. **Can we turn to PDX-4.4.**

15:29:16 **You also addressed expectations in your -- sales expectations in your direct; is that correct?**

15:29:23

15:29:25 A. **Yes.**

15:29:26 Q. **And the sales expectations we're looking at here, these were all created by Shire; is that right?**

15:29:30

15:29:32 A. **Yes.**

15:29:32 Q. **And it shows, you know, that the sales exceeded the expectations in all but one of those years?**

15:29:36

15:29:40 A. **Correct.**

15:29:40 Q. **And it's good for Shire when Shire exceeds its expectations; right?**

15:29:42

15:29:44 A. **Sure.**

15:29:46 Q. **All right. And you also looked at a third-party estimate for expectations from William Blair. That's PTX-148.**

15:29:50

15:29:55

15:30:00 **And you said that Shire exceeded William Blair's expectations as well; right?**

15:30:11

15:30:13 A. **Yes, and the consensus expectations.**

15:30:17 Q. **Right. Can I have 148.9.**

15:30:31 **And here, this report says William Blair is a market maker in the security of Shire and may have a long or**

15:30:35

15:30:38 short position.
15:30:39 A. Well, it says a market leader.
15:30:40 Q. Right. A market maker. It says, William Blair
15:30:44 intends to seek investment banking compensation in the next
15:30:47 three months from the subject company covered in this
15:30:50 report.
15:30:50 A. Sure.
15:30:52 Q. Can we go back to PDX-4.5.
15:31:08 Now, these are worldwide products; right? Not
15:31:15 U.S. products?
15:31:16 A. Yes.
15:31:17 Q. Is it your opinion that there's a nexus between the
15:31:21 '333 patent and sales outside the U.S.?
15:31:23 A. I've not formed an opinion in that regard. I've not
15:31:33 formed an opinion in that regard. I don't believe it's
15:31:36 necessary for me to reach my conclusions in this matter.
15:31:40 Q. You don't have an opinion that all of these profits
15:31:43 should be attributed to the '333 patent; is that right?
15:31:46 A. Well, I have an opinion that all of these profits are
15:31:51 derived from the sales of icatibant and whether it's in the
15:31:56 U.S. or globally, the attributes of icatibant are what has
15:32:02 made it safe and efficacious for the treatment of acute
15:32:05 attacks of HAE.
15:32:06 Q. Let's discuss the cost side of this as well. These
15:32:31 are the costs that are the difference between net sales and

15:32:34 operating income?
15:32:35 A. Yes, for the period from 2011 forward.
15:32:39 Q. And here, in 2011, this blue line below the horizontal
15:32:46 black line, that indicates a loss in 2011. Is that right?
15:32:50 A. That's correct, yes.
15:32:50 Q. Now, in preparing your report, you had access to Shire
15:32:59 costs from 2008 to 2010. Right?
15:33:02 A. Yes.
15:33:03 Q. And you didn't include those costs in the calculations
15:33:06 you provided here. Right?
15:33:07 A. That's correct. These are from the start of sales,
15:33:12 year of sales in the U.S.
15:33:13 Q. You also don't include costs associated with R&D from
15:33:17 before 2008. Correct?
15:33:19 A. Correct, although in that respect I don't believe I
15:33:23 had data or information.
15:33:24 Q. Right. You didn't include R&D costs incurred by
15:33:28 Hoechst and Aventis concerning the development of icatibant
15:33:32 before it was licensed to Jerini. Right?
15:33:35 A. Yes.
15:33:35 Q. You didn't include Shire and Jerini's R & D costs
15:33:40 through 2011?
15:33:41 A. Correct.
15:33:41 Q. Again, that wasn't a conscious decision to exclude
15:33:44 that information, you wanted to provide that information.

15:33:46 **Right?**

15:33:46 A. **Correct.**

15:33:47 Q. **New pharmaceuticals have to be approved by the FDA as being safe and efficacious before they can be sold in the U.S. Right?**

15:34:06 A. **That's true, for prescription drugs, yes.**

15:34:07 Q. **When the FDA approved Firazyr it approved the use of Firazyr to treat acute attacks of HAE?**

15:34:12 A. **Yes, that is my understanding.**

15:34:16 Q. **And it's that method of use that was shown to be safe and effective and therefore the reason the FDA approved the product?**

15:34:17 A. **Well, that use of icatibant to treat that condition, sure.**

15:34:24 Q. **And that approval is what led to the sales and profits that you testified about in your direct?**

15:34:29 A. **I think that's a fair characterization.**

15:34:35 Q. **And in that respect, it's the method of use that was tested and approved and enabled the sales and profits to be made?**

15:34:37 A. **No. In that respect, it is the molecule that has the attributes that allows it to be safe and effective for the treatment of acute attacks of HAE.**

15:34:40 **MR. SHERRY: Your Honor, I would like to call Mr. Bell's attention to some prior testimony.**

15:35:02 **THE COURT: Sure. Just point him in the direction so he can review it.**

15:35:23 **Is this a prior deposition?**

15:35:25 **MR. SHERRY: It is prior testimony here, Your Honor.**

15:35:27 **THE COURT: Given that he has been here four or five times, that wouldn't surprise me.**

15:35:33 **BY MR. SHERRY:**

15:35:36 Q. **Did you provide testimony in September 2016 in this court regarding a 40-milligram version of the drug Copaxone?**

15:35:39 A. **I believe so, with no representation as to the date, but, yes.**

15:35:46 Q. **Fair enough. And we have your testimony from there today. This is from the binder that has the transcript of the fifth day of the Copaxone trial, which is when you testified. And I will just direct you to Page 1204.**

15:35:49 **MR. SHERRY: Would you like us to give him a chance to review before we put this on the screen?**

15:35:53 **THE COURT: I would, yes. If you could direct him to the lines.**

15:35:59 **BY MR. SHERRY:**

15:36:02 Q. **If you could review the lines between 1204, Line 16, and -- 1205, Line 16?**

15:36:20 A. **I am sorry. 16 to 16?**

15:36:22 Q. **16 to 16. Once you have read that, I will ask you a**

15:36:24

15:36:26

15:36:27

15:36:28

15:36:33

15:36:38

15:36:39

more specific question.

A. Okay.

Q. Again, the Copaxone case concerned a method-of-use patent. Right?

A. Yes, it did.

MR. SHERRY: Can we bring that up on the screen, Your Honor?

THE COURT: Yes.

BY MR. SHERRY:

Q. I would like to direct your attention to Lines 5 through 12 on 1205. And you testified that "It's the method of use that was shown to be safe and efficacious and therefore the reason for the FDA to approve the product, and hence, that approval leads to the sales and profits in the U.S. that I have seen. In that respect, the nexus, IV, the method of use of the patent is the immediate method of use that was tested and approved and enabled the sales and profits to be made."

A. I did, yes, as appropriate in that circumstance.

Q. The FDA approved Firazyr with a single labeled indication, which was to treat acute attacks of HAE. Right?

A. Yes.

Q. Without that approval for treatment of acute attacks of HAE, there would have been no sales or profits associated with Firazyr. Right?

15:38:07 A. **Certainly not for that indication, sure, yes.**

15:38:10 Q. **There are no other indications that have been**

15:38:12 **approved. Correct?**

15:38:13 A. **Correct.**

15:38:13 Q. **In your analysis, you didn't attempt to attribute any**

15:38:21 **of -- you can take that down.**

15:38:23 **In your analysis, you didn't attempt to**

15:38:25 **attribute any of Firazyr's commercial performance for the**

15:38:29 **development of a method of using icatibant to treat HAE as**

15:38:33 **distinct from properties intrinsic to the icatibant**

15:38:35 **molecule?**

15:38:36 A. **Not as distinct from, correct.**

15:38:38 Q. **You didn't attribute any of Firazyr's commercial**

15:38:41 **performance to the formulation of Firazyr as distinct from**

15:38:44 **properties intrinsic to the icatibant molecule. Correct?**

15:38:47 A. **Again, not as distinct from, I think that's a fair**

15:38:50 **characterization.**

15:38:51 **MR. SHERRY: No further questions, sir.**

15:38:53 **THE COURT: All right.**

15:38:57 **MR. BLUMENFELD: Just a couple of questions,**

15:38:59 **Your Honor.**

15:39:00 **REDIRECT EXAMINATION**

15:39:01 **BY MR. BLUMENFELD:**

15:39:01 Q. **You were asked, Dr. Bell, some questions about, right**

15:39:08 **at the beginning of your cross-examination, about the price**

15:39:13 of Firazyr compared to other acute attack drugs. Do you
15:39:17 remember that?
15:39:18 A. Yes.
15:39:21 MR. BLUMENFELD: Your Honor, can I show the
15:39:22 witness and hand up PTX-141?
15:39:29 THE COURT: Yes.
15:39:45 BY MR. BLUMENFELD:
15:39:46 Q. Dr. Bell, can you tell us what PTX-141 is?
15:39:53 A. This is one of the standard reports that Shire would
15:39:58 produce from ZoomRx, which was the market research firm that
15:40:04 was used for what we call tracking studies, which would be
15:40:08 regular work with patients, regular market research work
15:40:16 with patients and physicians.
15:40:17 Q. Would you turn to Page 141.57. Can you tell us what
15:40:28 is shown on this page?
15:40:32 A. These are reasons for prescribing the different
15:40:42 products indicated for the treatment of acute attacks of HAE
15:40:48 on the left. And then on the right, issues that -- well,
15:40:55 specifically access issues that would prevent more
15:40:58 physicians from using each of the products.
15:41:01 Q. Let me ask you about the left side. What are the
15:41:04 acute attack products that are involved?
15:41:08 A. Here, they are looking at Firazyr, Berinert, and
15:41:11 Kalbitor.
15:41:12 Q. Do you see, a few lines below that it says, "The above

15:41:17 **chart presents the primary reason for prescribing that drug,**
15:41:21 **not necessarily the relative attribute ratings."**
15:41:24 **Do you see that?**
15:41:25 A. **Yes.**
15:41:25 Q. **Who was being asked the question about the reasons for**
15:41:30 **prescribing the drug?**
15:41:32 A. **Physicians.**
15:41:33 Q. **And do you see any indication anywhere on this chart**
15:41:40 **of physicians, prescribing physicians listing price as the**
15:41:44 **primary reason?**
15:41:46 A. **No. It's not listed for any of the products,**
15:41:51 **certainly not for Firazyr, and on the right-hand side, it's**
15:41:53 **actually making the point that access issues, which**
15:41:57 **potentially may have something to do with price, are reasons**
15:42:00 **why MD's aren't using more of the product.**
15:42:03 Q. **In the bar for Firazyr on the left side, there is 67**
15:42:08 **percent. Do you see that, Primary Reason? And what was**
15:42:12 **that reason?**
15:42:13 A. **Well, that's ease of administration.**
15:42:17 **MR. BLUMENFELD: Thank you very much. No**
15:42:18 **further questions.**
15:42:18 **THE COURT: All right. Thank you, Doctor. See**
15:42:20 **you again.**
15:42:21 **(Witness excused.)**
15:42:27 **MR. HAUG: Your Honor, we have one more short**

15:42:38 **deposition transcript of 15 minutes. I can play that. And**
15:42:42 **we have another live witness, if that is all right.**
15:42:45 **THE COURT: Yes.**
15:42:46 **MR. HAUG: The next testimony by deposition will**
15:42:49 **be of Aditi Dron, who is the regulatory affairs manager at**
15:42:57 **Fresenius, and was their designated 30(b)(6) witness on the**
15:43:02 **topic of Fresenius's decision to pursue and develop a**
15:43:06 **generic version of Firazyr.**
15:43:19 **May I hand up some binders?**
15:43:21 **THE COURT: Yes.**
15:43:32 **"Question: Could you please state your name**
15:43:33 **and address for the record?**
15:43:35 **"Answer: Aditi Dron, 5312 Galloway Drive,**
15:43:41 **Hoffman Estates, Illinois 60192.**
15:43:46 **"Question: Is there any reason that you can't**
15:43:48 **provide true and accurate answers today?**
15:43:50 **"Answer: No.**
15:43:51 **"Question: And I'm now handing you what's been**
15:43:54 **marked as Exhibit 3. It's the notice of deposition for**
15:44:03 **Fresenius Kabi, the 30(b)(6) notice. Do you recognize this**
15:44:08 **document?**
15:44:09 **"Answer: Yes.**
15:44:18 **"Question: Do you understand that you have been**
15:44:20 **designated as a witness to testify about certain topics**
15:44:24 **within this notice of deposition?**

15:44:25 **"Answer: Yes.**

15:44:29 **"Question: Do you understand that you were**
15:44:30 **designated to testify concerning Topic 8?**

15:44:42 **"Answer: Yes.**

15:44:43 **"Question: Well, Ms. Dron is also here in her**
15:44:47 **individual capacity, so Ms. Dron, to the extent you can tell**
15:44:54 **me from your personal knowledge, your interaction with Ms.**
15:45:01 **Schladt and her department, what's the -- what are the**
15:45:06 **typical stages of Fresenius's assessment of new products?**

15:45:15 **"Answer: At Fresenius Kabi USA new products are**
15:45:19 **assessed by -- or at least the responsibility for**
15:45:22 **coordination of these assessments lies with the portfolio**
15:45:28 **management group; however, it is a collective activity and**
15:45:32 **decision involving multiple departments and roles.**

15:45:41 **"Question: Okay. And how typically -- who**
15:45:48 **presents typically a new idea from the beginning?**

15:45:58 **"Answer: For example, for icatibant portfolio,**
15:46:04 **management follows the process called new project approval.**
15:46:11 **There are multi-faceted information that are collected about**
15:46:19 **the target molecule and they are compiled into a new project**
15:46:34 **approval package. This package is reviewed and assessed by**
15:46:38 **a multi-disciplinary high level team and based on their**
15:46:42 **assessment either these get approved or they do not get**
15:46:53 **approved.**

15:46:54 **"Question: With respect to icatibant prior to**

15:47:03 **undergoing the new product approval process, where does the**
15:47:08 **idea of -- well, strike that.**
15:47:12 **"Prior to the new product approval process for**
15:47:19 **icatibant, what department was responsible at Fresenius for**
15:47:30 **deciding icatibant should undergo that process?**
15:47:43 **"Answer: I think it initiates there in**
15:47:45 **portfolio management.**
15:47:47 **"Question: So it initiates with Ms. Schladt's**
15:47:50 **group?**
15:47:51 **"Answer: I believe so.**
15:47:56 **"Question: And do you know what type of**
15:48:00 **research Ms. Schladt's group, portfolio management,**
15:48:04 **undertook with respect to icatibant in terms of deciding**
15:48:08 **icatibant would undergo the new product approval process?**
15:48:12 **"Answer: Yes.**
15:48:17 **"Question: Okay. And what -- what did they do?**
15:48:22 **"Answer: It involves detailed financial**
15:48:24 **analysis, regulatory review, active pharmaceutical**
15:48:27 **ingredient sourcing, legal review and assessment,**
15:48:30 **manufacturing and operations review and assessment,**
15:48:42 **strategic fit within the portfolio assessment, and there may**
15:49:05 **be some that I may have missed.**
15:49:07 **"Question: Okay. And what documentation is**
15:49:17 **generally -- or is generated with respect to this new**
15:49:25 **product approval process, and we can focus on icatibant?**

15:49:29 **"Answer: It's called the NPA. I mentioned new**
15:49:32 **project approval before. So that's the terminology that's**
15:49:36 **used for that information package.**
15:49:43 **"Question: Oh, I've been told that I'm calling**
15:49:47 **it new product approval. Is it new product approval or new**
15:49:51 **project approval process?**
15:49:54 **"Answer: I believe it's new project.**
15:50:03 **"I am calling it NPA.**
15:50:06 **"Question: We can -- how about we call it NPA,**
15:50:10 **and whether it's project or product, I think we were all**
15:50:12 **talking about the same thing, so I think we're clear.**
15:50:16 **"And when was the NPA approved, do you know?**
15:50:20 **"Answer: Yes, the NPA was approved in July**
15:50:23 **2014.**
15:50:26 **"Question: Ms. Dron, I'm going to hand you now**
15:50:30 **what's been marked as Exhibit 7. It's Bates-stamped as FKIA**
15:50:36 **4572 through 4575.**
15:50:44 **"Ms. Dron, this is -- excuse me -- a January**
15:50:53 **3rd, 2014 e-mail from Jay Kao at Fresenius. Do you**
15:51:02 **recognize this e-mail?**
15:51:04 **"Answer: Yes, I do.**
15:51:06 **"Question: Oh, and how do you recognize the**
15:51:13 **e-mail?**
15:51:16 **"Answer: What I meant is that I can -- I can**
15:51:19 **read it. I have not seen it before.**

15:51:21 **"Question: Oh, thank you.**

15:51:23 **"In what department is Lindsay Thomas in at**

15:51:28 **Fresenius?**

15:51:29 **"Answer: Lindsay Thomas is in marketing.**

15:51:31 **"Question: Thank you.**

15:51:33 **"Do you have an understanding, Ms. Dron, of what**

15:51:36 **Fresenius was doing in its pursuit of icatibant from**

15:51:41 **September 2013, which was the time frame of Exhibit 6, until**

15:51:50 **the date of this e-mail in January of 2014?**

15:52:01 **"Answer: I believe Fresenius was collecting**

15:52:03 **data and preparing assessment for the new project's**

15:52:06 **approval.**

15:52:07 **"Question: And, Ms. Dron, I have marked**

15:52:12 **Exhibit 10, which is an e-mail with three attachments,**

15:52:18 **ranging from FKIA 18,646 to 19,554.**

15:52:36 **"Actually, I just called it an e-mail, but it's**

15:52:41 **a meeting invite, excuse me. If you could just tell me,**

15:52:45 **have you seen this meeting invite before? You don't need to**

15:52:49 **look at all the attachments. Just let me know if you have**

15:52:53 **seen the meeting invite.**

15:52:59 **"Answer: No, I have not seen this before.**

15:53:00 **"Question: The subject says icatibant pre-feas.**

15:53:08 **My understanding is that pre-feas would be pre-feasibility.**

15:53:14 **Is that your understanding?**

15:53:17 **"Answer: Yes, it is.**

15:53:19 **"Question: Do you know what pre-feasibility**
15:53:22 **stands -- means? Is that a stage of your NPA process?**
15:53:28 **"Answer: Pre-feasibility in my understanding**
15:53:34 **would be referring to a time during which an NPA packet is**
15:53:40 **being proposed, research is being conducted, so it's a**
15:53:47 **different time frame before -- before -- while the product**
15:54:02 **is being considered and it has actually not been approved as**
15:54:10 **a project to actually start working on.**
15:54:14 **"Question: -- you can see that he mentions,**
15:54:19 **dear all, and then he goes on to say this one has an urgent**
15:54:24 **NCE-1 date of August 2015; do you see that?**
**"Answer: Yes.**
15:54:34 **"Question: Is the NCE-1 date the date that**
15:54:43 **Fresenius was seeking to meet for submitting their icatibant**
15:54:51 **ANDA to the FDA?**
15:54:53 **"Answer: Yes.**
15:54:53 **"Question: And is -- NCE-1 is the first date**
15:54:57 **that a generic could file for icatibant; correct?**
15:55:05 **"Answer: Yes, that is my understanding.**
15:55:07 **"BY MS. CHUBB:**
15:55:16 **"Question: Ms. Dron, I am marking Exhibit 27,**
15:55:19 **which is Bates numbered FKIA 27532 to 533. It's a**
15:55:27 **September 1st, 2014, e-mail from Nicole Pansy. Do you**
15:55:32 **recognize this e-mail, Ms. Dron?**
**"Answer: Yes.**

15:55:38 **"Question: And the subject is icatibant PFS**
15:55:53 **U.S. start workshop dates. What is a start workshop, Ms.**
15:56:18 **Dron?**
15:56:19 **"Answer: I would describe a start workshop as**
15:56:23 **one of the first meetings or a kickoff meeting for a project**
15:56:31 **where all the core team members are invited, and it is a**
15:56:36 **first in a series of meetings that are held for achieving a**
15:56:45 **certain goal of the project.**
15:56:48 **"Question: Okay. And in terms of kind of a**
15:57:02 **timeline of a project's stages, is it fair to say that there**
15:57:06 **is a feasibility stage that then moves to an approved stage,**
15:57:13 **that then begins with this start workshop once the project**
15:57:19 **is approved? Or if that's not an accurate portrayal, can**
15:57:28 **you help with the general stages that begin before the start**
15:57:37 **workshop or that happen before that?**
15:57:40 **"Answer: So I agree with what you said.**
15:57:43 **Starts with feasibility and then moves on to becoming a**
15:57:46 **project once the NPA's approved, and then the project work**
15:57:51 **begins and start workshop would be in the beginning of the**
15:57:56 **actual work to develop the project -- or to develop the**
15:57:59 **product.**
15:58:00 **"Question: Okay. And, Ms. Dron, you have no**
15:58:04 **reason to doubt this is a true and accurate copy of an**
15:58:07 **e-mail created and maintained by Fresenius in the ordinary**
15:58:19 **course of this business?**

15:58:20 "Answer: No doubt."
15:58:21 (End of videotaped deposition.)
15:58:31 MR. HAUG: Plaintiffs call as their next witness
15:58:36 Dr. Renate Wingefeld.
15:58:39 THE COURT: Okay.
15:58:59 ... RENATE WINGEFELD, having been duly
15:59:24 sworn as a witness, was examined and testified
15:59:26 as follows ...
15:59:37 THE COURT: Good afternoon.
15:59:38 THE WITNESS: Good afternoon.
15:59:41 MR. HAUG: We have some heavy binders. I'm
15:59:43 sorry.
15:59:43 (Binders handed to the Court and to the
15:59:45 witness.)
16:00:28 MR. HAUG: May I begin, Your Honor?
16:00:31 THE COURT: Yes.
16:00:32 DIRECT EXAMINATION
16:00:34 BY MR. HAUG:
16:00:35 Q. Good afternoon, Dr. Wingefeld.
16:00:36 A. Good afternoon.
16:00:37 Q. Where do you reside?
16:00:38 A. I reside in Geisenheim in Germany.
16:00:45 Q. And what is your current occupation?
16:00:46 A. I'm a senior counsel at Sanofi, Sanofi Aventis Pharma
16:00:54 Deutschland. I'm in the intellectual property department in

16:01:02 **the Pharma Group in Frankfurt, Germany.**

16:01:06 Q. **How long have you been with Sanofi Aventis Deutschland**

16:01:11 **GmbH?**

16:01:13 A. **I have been with this company and predecessor**

16:01:16 **companies for more than 30 years now.**

16:01:18 Q. **And were you in a particular department at Sanofi**

16:01:21 **Aventis?**

16:01:22 A. **Yes. I started in the Pharma Patents Department.**

16:01:28 **That's the same department as I'm now. Now it's called the**

16:01:31 **Global Intellectual Property Department.**

16:01:33 Q. **And what are your basic responsibilities as senior**

16:01:38 **counsel in the Pharma Patents Or Intellectual Property**

16:01:43 **Department?**

16:01:44 A. **I oversee drafting, filing and prosecution of the**

16:01:50 **patent applications worldwide. I handle also petition**

16:01:58 **papers and patent registration papers and also license**

16:02:02 **agreements with regard to IP matters on the project I'm**

16:02:07 **working with.**

16:02:08 **I communicate with outside prosecution counsel,**

16:02:16 **and I advise and counsel the scientists and other clients**

16:02:21 **from our company on IP matters.**

16:02:24 Q. **What is your educational background following the**

16:02:29 **equivalent of high school?**

16:02:30 A. **After high school, in 1976 I started studying**

16:02:40 **chemistry at the University of Giessen in Germany. I**

16:02:45 received my diploma in 1982. And then I started a Ph.D.
16:02:54 program also at this University. I received my Ph.D. in
16:03:00 inorganic chemistry in 1985, and in 1993, I became a
16:03:08 European patent attorney.
16:03:10 Q. Do you have to take an exam of any kind to become a
16:03:15 European patent attorney?
16:03:17 A. Yes. I had to take an exam, and I also had to work in
16:03:23 a patent department for several years.
16:03:26 Q. What did you study as you were becoming a Ph.D.?
16:03:31 A. I studied chemistry and I received my diploma in
16:03:38 inorganic chemistry.
16:03:43 Q. Approximately, how many U.S. patent applications have
16:03:46 you been involved in prosecuting during your career?
16:03:52 A. Those are approximately 300 U.S. patent applications.
16:03:59 Q. How many of those applications have been in the
16:04:01 pharmaceutical area?
16:04:02 A. That would be almost all.
16:04:06 Q. Are you familiar with U.S. Patent 5,648,333?
16:04:16 A. Yes.
16:04:17 Q. And you can actually, if you would please look at one
16:04:21 of your binders, JTX-1. That's the smallest one.
16:04:31 A. Yes.
16:04:31 Q. Volume 3 of 3. It's the smallest one.
16:04:35 A. Yes.
16:04:41 Q. And do you recognize JTX-1?

16:04:45 A. **I'm sorry.**

16:04:54 Q. **Right. It's the smaller binder.**

16:04:56 A. **Oh.**

16:04:58 Q. **The tabs are on the side. Do you see that, JTX?**

16:05:02 A. **One?**

16:05:02 Q. **One.**

16:05:06 A. **Oh, I'm sorry. Yes.**

16:05:09 Q. **Okay. Do you recognize that document?**

16:05:12 A. **Yes.**

16:05:13 Q. **What is it?**

16:05:15 A. **This is the certified copy of the U.S. Patent 5,648,333.**

16:05:23 Q. **Is it okay, is it acceptable to you if I refer to this document as the '333 patent?**

16:05:30 A. **Yes.**

16:05:32 Q. **Thank you.**

16:05:33 **How did you become familiar with the '333 patent, Dr. Wingefeld?**

16:05:37 A. **I was the in-house prosecuting attorney for this '333 patent. I was responsible for the initial filing of this priority document, so I think from the beginning.**

16:06:01 Q. **Who drafted the original patent application which ultimately became the '333 patent?**

16:06:08 A. **I did.**

16:06:10 Q. **Were you responsible for prosecuting the '333 patent**

16:06:14 **from initial filing in the U.S. to issuance?**

16:06:18 A. **Yes. However, there was some point when I was on**

16:06:25 **maternity leave, where I didn't work at all.**

16:06:30 Q. **Do you recall when that was?**

16:06:31 A. **Yes. That was from July '92 until July '93.**

16:06:38 Q. **Dr. Wingefeld -- withdrawn.**

16:06:44 **I would like you to go to JTX-1.2. That's the**

16:06:48 **second page.**

16:06:50 A. **Yes.**

16:06:51 Q. **Do you know when the first application was filed that**

16:06:56 **led to the '333 patent?**

16:06:58 A. **Yes. The first application was filed in the U.S. on**

16:07:07 **June 30th, 1989.**

16:07:09 Q. **And do you know when the patent issued?**

16:07:12 A. **Yes. It issued on July 15th, 1997.**

16:07:16 Q. **And looking still at this page of JTX-1.2, who are the**

16:07:25 **inventors?**

16:07:26 A. **The inventors are Stephen Henke, Gerhard Briepohl,**

**Jochen Knolle, Jens Stechl, Bernward Scholkens, Hans-Wolfram**

16:07:43 **Fehlhaber, Hermann Gerhards and Franz Hock.**

16:07:45 Q. **Do you know where the inventors were residing at the**

16:07:48 **time of the filing of this patent application?**

16:07:50 A. **All were residing in Germany.**

16:07:54 Q. **And do you know, are you familiar with a company**

16:07:57 **called Hoechst?**

16:07:58 A. **Yes, of course.**

16:08:00 Q. **And what is Hoechst?**

16:08:01 A. **Hoechst is a pharmaceutical company. At that time, it**
16:08:06 **was a chemical company.**

16:08:09 Q. **Is it related to Sanofi?**

16:08:11 A. **Yes. It's the predecessor company of Sanofi.**

16:08:14 Q. **And where was Hoechst AG located at the time of the**
16:08:17 **filing of the patent application?**

16:08:19 A. **It was located in Frankfurt Main, in Germany.**

16:08:27 Q. **Can you tell me who were the U.S. prosecuting**
16:08:30 **attorneys for the '333 patent?**

16:08:33 A. **Yes. This was the Finnegan firm. Finnegan,**
16:08:42 **Henderson, Farabow, Garrett & Dunner.**

16:08:42 Q. **And if you would stay on this page and go to the**
16:08:44 **left-hand column where it says, related U.S. applications**
16:08:47 **data.**

16:08:48 **Do you see that?**

16:08:49 A. **Yes.**

16:08:49 Q. **It's also on the screen in front of you.**

16:08:53 **And what is this section of the patent informing**
16:08:57 **you?**

16:08:57 A. **Oh, those show all of the patent applications which**
16:09:03 **finally led to the '333 patent.**

16:09:10 Q. **And based on your experience in prosecuting U.S.**
16:09:13 **patents, was the '333 patent prosecution more or less**

16:09:19 **complicated than the average application you handled as far**
16:09:23 **as the number of applications that were filed?**
16:09:25 A. **Yes. It definitely was.**
16:09:27 Q. **Definitely was what?**
16:09:29 A. **Was more complicated.**
16:09:31 Q. **Okay. Please move down on the left-hand column to the**
16:09:38 **next section where it says foreign application priority**
16:09:42 **data.**
16:09:42 **Do you see that?**
16:09:43 A. **Yes.**
16:09:43 Q. **And what is the information contained there? What**
16:09:46 **does that say?**
16:09:46 A. **This shows the priority data which were filed before**
16:09:54 **those patent applications were filed in the U.S., and those**
16:10:00 **were the initial filings which led to the '333 patent.**
16:10:07 Q. **Are these patent applications that were filed in**
16:10:11 **Germany?**
16:10:12 A. **Yes.**
16:10:12 Q. **What was Hoechst's goal in the prosecution of the '333**
16:10:23 **patent, if you know?**
16:10:24 A. **The goal was, as it is always, to get all claims**
16:10:31 **allowed where a patent application is applied for.**
16:10:41 Q. **Did you meet with the inventors when you were drafting**
16:10:44 **the first patent application?**
16:10:45 A. **Yes, I did. We had a designated inventor out of this**

16:10:55 **group, who I mainly was working with.**

16:10:58 Q. **And you mentioned that it was the goal of Hoechst to**

16:11:07 **acquire patent protection for all of the claims that they**

16:11:11 **were applying for; is that right?**

16:11:12 A. **Yes.**

16:11:13 Q. **And were the actions taken during the prosecution of**

16:11:16 **the '333 patent consistent with that goal?**

16:11:19 A. **Yes.**

16:11:20 Q. **What was the general approach used by Hoechst at this**

16:11:29 **time at the filing of this patent application to protect**

16:11:32 **inventions within the company?**

16:11:34 A. **Oh, the procedure was that the, all the inventors,**

16:11:43 **they are required to file an information disclosure to the**

16:11:48 **company, and then the company will decide if they want to**

16:11:54 **claim it and want to file it at present. If they don't**

16:11:59 **decide to file it, then it's up to the inventor. They can**

16:12:04 **go for filing and pursuing a patent on their invention.**

16:12:11 **So in this case we decided to file a patent on**

16:12:18 **this one, and then we -- so I did then work together with**

16:12:27 **the designated inventor, to work out the specification and**

16:12:33 **drafting the claims for the first initial German priority**

16:12:38 **filing.**

16:12:45 Q. **Do the inventors for this patent -- withdrawn.**

16:13:00 **Are the inventors for this patent entitled to**

16:13:01 **any remuneration?**

16:13:04 A. **Yes, they are.**

16:13:04 Q. **Just generally, what is your understanding of remuneration to which they are entitled?**

16:13:07 A. **They get reimbursed later on, on the profit, what comes out of the patent.**

16:13:11 Q. **Do the inventors have any say during the prosecution?**

16:13:17 A. **Yes. So when they file this invention disclosure and they would show what the invention is, then when we want to limit the claims perhaps, then we have to ask them first, because we cannot just do it as a company from ourselves to make any changes to the claim and to what's in the specification, what's in the -- what the invention was, we cannot limit the invention ourselves.**

16:13:19 Q. **So still looking at JTX-1, which is the cover page of the '333 patent, can you tell us what the first priority document was that you prepared?**

16:13:24 A. **The first priority document that was filed on November 24th, 1988, it has the German Patent Application No. 3839581.9.**

16:13:33 Q. **Does the '333 patent as it issued, does it include the disclosures from each of these five foreign German applications?**

16:13:39 A. **Yes, it does.**

16:13:44 Q. **And the inventors, which we saw before, are they the inventors that participated in the disclosures in one or**

16:13:49

16:13:53

16:13:57

16:14:00

16:14:08

16:14:13

16:14:16

16:14:22

16:14:38

16:14:41

16:14:47

16:14:51

16:14:52

16:14:53

16:14:58

16:15:05 more of these five applications?
16:15:06 A. Yes.
16:15:07 Q. So is it the case that the inventors may not be
16:15:11 inventors on all the claims that ultimately issued?
16:15:14 A. Yes.
16:15:14 Q. Did you prepare -- did you review the file histories
16:15:24 for all of these -- all of these file histories which are
16:15:27 listed in the '333 patent, have you reviewed these file
16:15:31 histories in preparation for this testimony?
16:15:32 A. Yes, I did.
16:15:33 Q. I am not going to ask you how many pages they are.
16:15:36 But I would ask you how you reviewed them and analyzed them
16:15:42 in preparation for your testimony today?
16:15:46 A. I looked at the file histories in these two binders,
16:15:55 and I looked through all these pages, and -- and prepared
16:16:01 for this.
16:16:03 Q. Did you prepare a summary?
16:16:06 A. Yes.
16:16:07 Q. You should have a white binder.
16:16:12 A. Yes. I did this because, as I told you earlier, it's
16:16:22 a very complex situation, the file history. So I did this,
16:16:32 which I think this chart, which is PDX5.1, will help me to
16:16:44 explain what happened.
16:16:48 MR. HAUG: Your Honor, may I put a blowup of
16:16:51 this particular chart up?

16:16:53 **THE COURT: Yes.**

16:16:54 **MR. HAUG: Thank you very much.**

16:17:10 **BY MR. HAUG:**

16:17:10 Q. **This is just an enlarged copy of PDX-5.1, if that is**
16:17:16 **easier to see, I am not sure it is. It is a little bit far**
16:17:19 **away.**

16:17:26 **I would like you to turn to Volume 1 of 3. This**
16:17:29 **is one of the big binders. And there are a number of**
16:17:41 **exhibits in this binder. Let's start with the first one.**
16:17:45 **And can you -- do you know what JTX-2 is?**

16:17:50 A. **Yes.**

16:17:50 Q. **What is it?**

16:17:52 A. **JTX-2 is the file history of the U.S. Application**
16:18:03 **08/487,442, and this includes, also, this is the file**
16:18:14 **history of this section that's shown on this chart in purple**
16:18:24 **at the very end of Group 1.**

16:18:26 Q. **What is the number on that chart that you have? 5.1?**

16:18:32 A. **5.1.**

16:18:33 Q. **What is the U.S. serial number, just so the record is**
16:18:36 **clear?**

16:18:38 A. **U.S. Serial Number is 08/487,442.**

16:18:42 Q. **What is the next exhibit in this binder, which is**
16:18:46 **JTX-6?**

16:18:52 A. **This is the file history of U.S. Serial No.**
16:18:58 **07/982,052.**

16:19:05 Q. **Where does that appear on your chart PDX-5.1?**

16:19:10 A. **This appears on the chart in the Group 1, which is depicted in green.**

16:19:23 Q. **There is one more exhibit in this big binder, JTX-7. What is that, if you know?**

16:19:31 A. **That is the file history of U.S. Patent Application 08/236,018. That's the file history of those two applications depicted in purple, which are shown as U.S. Serial No. 08/236,018 and U.S. Serial No. 08/012,849.**

16:20:00 Q. **Now, looking at your chart, PDX-5.1, you set forth Group 1, Group 2 and Group 3. Do you see that?**

16:20:12 A. **Yes.**

16:20:12 Q. **Could you please explain to the Court what Group 1, Group 2 and Group 3 represent?**

16:20:18 A. **Okay. So we have filed three groups of independent and distinct inventions, the Group 1 depicted in green, the Group 2, depicted in blue, and the Group 3, depicted in pink. And at a certain point during prosecution, we consolidated those three groups into a patent application, and this consolidated group is depicted in purple here.**

16:21:02 Q. **What is the serial number of the consolidated patent application?**

16:21:08 A. **The serial number is U.S. 08/012,849.**

16:21:15 Q. **And when was that filed?**

16:21:16 A. **This was filed on February 3rd, 1993.**

16:21:20 Q. **What is the first application that you filed that**
16:21:28 **contains all of the subject matter which is contained in the**
16:21:32 **'333 patent which issued?**
16:21:36 A. **The first application was filed containing, comprising**
16:21:40 **all the subject matter of those invention -- of the three**
16:21:45 **inventions, was the U.S. Application No. 08/012,849.**
16:21:53 Q. **And that's all the one at -- the top one in purple.**
16:21:58 **Is that right?**
16:21:58 A. **Yes.**
16:21:58 Q. **And you said that the Groups 1, 2 and 3 represent**
16:22:04 **independent and distinct inventions. What do you mean by**
16:22:08 **that?**
16:22:10 A. **Those -- so we had received three independent**
16:22:18 **invention disclosure forms. So we filed three independent**
16:22:24 **groups of priority applications, and we also prosecuted them**
16:22:31 **outside the U.S. as independent patent groups.**
16:22:37 **MR. WIESEN: Your Honor, I don't mean to cut off**
16:22:38 **the witness. I have a discovery-related objection. To the**
16:22:41 **extent we get into the invention disclosures as a basis, I**
16:22:45 **don't believe they have been produced in the case.**
16:22:48 **MR. HAUG: Other than asking the witness what**
16:22:49 **the process was, I am not asking anything about them.**
16:22:52 **MR. WIESEN: With that, that's fine. I didn't**
16:22:54 **know whether we were about to get into the details, Your**
16:22:57 **Honor.**

16:22:57 **THE COURT: Apparently not.**

16:23:02 **THE WITNESS: So we prosecuted Groups 1, 2 and 3 separately, because they were related to the different invention disclosure forms.**

16:23:21 **BY MR. HAUG:**

16:23:22 Q. **Groups 1, 2 and 3 were being prosecuted separately. Is that what you are saying?**

16:23:27 A. **Yes.**

16:23:27 Q. **And then did all three of these groups come together in the consolidated application which you just referred to as the '849 application?**

16:23:37 A. **Yes.**

16:23:37 Q. **That was in February of 1993. Is that correct?**

16:23:42 A. **That's correct.**

16:23:42 Q. **Do the three groups have different priority dates?**

16:23:57 A. **Yes, they have.**

16:24:01 **So Group 1 has three different priority dates. The first one is DE P 38 39 581.9 filed on November 24th, 1988.**

16:24:23 **The second one in this Group 1 is DE P 39 16 291.5, filed on May 19th, 1989. And the third one to Group 1 is DE P 39 18 225.8, filed on June 3rd, 1989.**

16:24:57 **Those three priority patent applications resulted in the first U.S. patent application with Serial No. 07/374,162.**

16:25:18 Q. **Are you finished? What is the priority date for the**
16:25:20 **Group 2 applications?**
16:25:21 A. **For Group 2, the priority date is August 14th, 1989.**
16:25:30 **It was filed as German Patent Application 39 26 822.5.**
16:25:38 Q. **And what is the priority date for the Group 3**
16:25:41 **applications?**
16:25:42 A. **Group 3 was filed, priority application was filed on**
16:25:47 **April 26th, 1990, in a German priority patent application**
16:25:54 **with the No. 40 13 270.6.**
16:25:59 Q. **And was the inventorship different for Groups 1, 2 and**
16:26:03 **3?**
16:26:04 A. **Yes.**
16:26:09 Q. **Was this -- was the filing of separate groups and**
16:26:16 **separate prosecution, was that a typical practice in your**
16:26:19 **experience?**
16:26:19 A. **Yes.**
16:26:20 Q. **Dr. Wingefeld, please turn to the first binder, which**
16:26:29 **I gave you, that has JTX -- let me try to do this**
16:26:36 **differently.**
16:26:37 **I am going to try to be as quick as we can. We**
16:26:40 **are not going to walk through all of these applications. I**
16:26:43 **think the Court has already seen the applications.**
16:27:00 **Turning back to your chart, on PDX5.1, do you**
16:27:05 **see the designation of CIP?**
16:27:08 A. **Yes.**

16:27:09 Q. **What do you mean by CIP?**

16:27:12 A. **CIP is a continuation-in-part application.**

16:27:18 Q. **What is a continuation-in-part application?**

16:27:21 A. **That's an application where you add new matter, and you claim the priority of the prior application.**

16:27:32 Q. **What do you mean by new matter?**

16:27:36 A. **New matter can be, for instance, new examples, it could also be new data, like IC50 data.**

16:27:51 **We also, new matter -- so we added new claims, you can add new claims or amend claims.**

16:28:01 Q. **Was the use -- withdrawn.**

16:28:03 **Was the filing of continuation-in-part applications a common practice that you engaged in?**

16:28:10 A. **Yes, very.**

16:28:14 Q. **Did you add data and examples when you filed the '149 CIP application?**

16:28:34 A. **Yes, we did.**

16:28:35 Q. **Can you identify where the '149 application is on your chart?**

16:28:37 A. **On my chart, the '149 application is in Group 1, the third one, in the middle row from the top.**

16:28:46 Q. **Was the '149 -- is that a CIP application?**

16:28:52 A. **Yes, it is a CIP.**

16:29:00 Q. **And was that filed after receiving an office action in the '162 application?**

16:29:03

16:29:04

16:29:08

16:29:11 A. **Yes.**

16:29:11 Q. **What was the next application that Hoechst filed in Group 1?**

16:29:16 A. **In Group 1 we filed then a continuation application, which led to the U.S. patent application 07/982,052, and we filed this on November 25th, 1992.**

16:29:22 Q. **Now, you mentioned a continuation application. Is that represented by "Con" here?**

16:29:34 A. **Yes.**

16:29:38 Q. **What is a continuation application?**

16:29:40 A. **That is an application where you maintain the priority date, and this application then becomes automatically -- the prior application becomes automatically abandoned.**

16:29:43 Q. **Was it a common practice to file continuation applications?**

16:29:52 A. **Yes, very.**

16:29:59 Q. **Can you approximate, of the 300 or so patent applications that you have prosecuted in the U.S., how many times would you file continuation applications in each of those, or any of those?**

16:30:02 A. **We did this at the time when we prosecuted the '333 patent about -- we did this like maybe 80 percent.**

16:30:05 Q. **80 percent --**

16:30:05 A. **60-80 percent, yeah.**

16:30:06 Q. **Now, are you familiar with the appeal process in the**

16:30:10

16:30:13

16:30:16

16:30:21

16:30:31

16:30:36

16:30:38

16:30:41

16:30:57 **Patent Office?**

16:30:58 A. **Yes.**

16:30:58 Q. **And so if you received -- you received office actions in the '333 patent prosecution. Isn't that right?**

16:31:03

16:31:06 A. **Yes.**

16:31:06 Q. **Okay. When you receive an office action, did you ever appeal any of those office actions?**

16:31:10

16:31:14 A. **Yes, I did.**

16:31:15 Q. **I mean in the '333 patent?**

16:31:19 A. **In the '333, no. In the '333 we didn't do it because it was the Hoechst strategy not to -- to go on with the prosecution, and not to step into an appeal process, which is a very lengthy process.**

16:31:25

16:31:40

16:31:47

16:31:49 Q. **Well, based on your experience, in the time frame of 1990 to 1995, how long would an appeal take from an office action if you didn't agree with the office action?**

16:31:53

16:31:59

16:32:03 A. **To my experience, it was around, depending on the specific case, but around three years it took to get a decision.**

16:32:10

16:32:15

16:32:15 Q. **So if you filed an appeal from an office action, would the prosecution just stop?**

16:32:19

16:32:21 A. **Yes.**

16:32:21 Q. **During the pendency of the appeal?**

16:32:23 A. **Yes.**

16:32:23 Q. **So what is an alternative to filing an appeal if you**

16:32:28 receive an office action that you don't agree with?
16:32:31 A. The alternative is definitely to file a continuation
16:32:40 application, and there are -- yes.
16:32:51 Q. Now, I would like to focus your attention --
16:32:55 MR. WIESEN: Your Honor, I hate to object.
16:32:57 Could we be heard at sidebar on an issue that I am afraid we
16:33:00 might get into, if Mr. Haug -- I don't want to do it in
16:33:03 front of the witness.
16:33:04 (Sidebar conference held as follows.)
16:33:04 THE COURT: Yes, Mr. Wiesen?
16:33:06 MR. WIESEN: I'm afraid we're going to go into
16:33:08 an explanation that was not provided in discovery for why
16:33:13 the prosecution took as long as it did.
16:33:15 Dr. Wingefeld was the 30(b)(6) deponent, the
16:33:19 designee of the company, and when we asked her why they
16:33:22 didn't respond to particular applications and why they filed
16:33:24 continuations and CIPs, all we got was an "I don't know" and
16:33:28 "I don't recall." To the extent what he's doing is setting
16:33:31 the foundation for a new explanation that we've not heard
16:33:34 before, I think that's inappropriate, especially in the
16:33:38 context of a 30(b)(6) designee.
16:33:41 MR. HAUG: I'm only asking, I was only asking
16:33:44 the witness based on her experience what typical response
16:33:47 would be to an office action. It wasn't specific to the
16:33:51 '333.

16:33:53 **MR. WIESEN: I certainly agree with that, and if**
16:33:55 **he's representing that that is not going to be the testimony**
16:33:58 **she gives and the argument that they make, then that's fine,**
16:34:01 **but if she's going to go further --**
16:34:03 **THE COURT: It doesn't sound like he intends to**
16:34:05 **do that.**
16:34:06 **MR. HAUG: I don't.**
16:34:06 **MR. WIESEN: That was why I wanted to do it at**
16:34:08 **sidebar, and if that's the representation, then I have no**
16:34:11 **objection.**
16:34:12 **THE COURT: Okay.**
16:34:28 **(End of sidebar conference.)**
16:34:38 **BY MR. HAUG:**
16:34:38 Q. **I'd like to focus your attention on the '052**
16:34:41 **application in the Group 1.**
16:34:43 **Do you see that?**
16:34:43 A. **Yes.**
16:34:44 Q. **Okay. And your chart says that you filed the '849**
16:34:52 **CIP.**
16:34:52 **Do you see that?**
16:34:53 A. **Okay. I see it.**
16:34:54 Q. **Okay. Again, why did you file the '849 CIP**
16:34:58 **application?**
16:34:58 A. **We received obvious-type double patenting rejections**
16:35:10 **in this, in this '052, this Group 1 application, and we also**

16:35:16 received obvious-type double patenting rejections and office
16:35:22 actions from the Group 2 and Group 3 patent applications,
16:35:27 which were pending. And so we -- we, from reviewing the
16:35:34 files, we decided to file this, a patent application and as
16:35:43 a consolidated patent application wherein we combined the
16:35:50 claims of Group 1, Group 2 and Group 3 applications.
16:35:55 Q. So are the three groups consolidated in order to
16:36:01 overcome the obviousness-type double patenting rejection
16:36:04 that was raised by the office; is that right?
16:36:06 A. Yes. This is right, and we also did this to expedite
16:36:12 the prosecution of the independent patent application.
16:36:21 Q. Would you please turn to JTX-7.11, Page 11.
16:36:31 A. Yes.
16:36:32 Q. That's in Volume 1 of 3.
16:36:51 A. Yes.
16:36:52 Q. Okay. And if you turn, what claims are in this
16:36:59 application? This is the '849 application; is that right?
16:37:01 A. This is the '849 application, which was filed on
16:37:06 February 3rd, 1993. And there were the claims from the
16:37:17 previous patent application from Group 1, Group 2 and
16:37:21 Group 3. All the claims were combined in the main claim.
16:37:28 Q. And do the claims that eventually issued in the '333
16:37:32 patent cover all three of these groups as consolidated into
16:37:36 this application?
16:37:37 A. Yes.

16:37:38 Q. **After combining the three groups, what happened next in the prosecution?**

16:37:49 A. **Thereafter, we filed a continuation application, which is the '018 patent application. We filed this on May 2nd, 1994.**

16:38:08 Q. **And did you take any additional actions in the '018 application with respect to the office action that had been issued by the Patent Office?**

16:38:17 A. **Yes, we did.**

16:38:19 Q. **What were your next steps?**

16:38:20 A. **The next step was that we conducted an examiner interview.**

16:38:22 Q. **Where was the interview held?**

16:38:33 A. **This interview was held in Washington, at the USPTO.**

16:38:34 Q. **Was it a common practice of yours to conduct interviews with examiners at the USPTO?**

16:38:36 A. **No. That was the only time that in my more than 30-year career that I conducted personally an interview at the USPTO.**

16:38:40 Q. **So you traveled to Washington, D.C. for that?**

16:38:45 A. **Yes.**

16:38:52 Q. **Who went to that interview?**

16:38:57 A. **Oh, that was me and the -- my counsel from Finnegan Henderson.**

16:38:58 Q. **Please turn to JTX-7.261, please.**

16:39:01

16:39:01

16:39:03

16:39:13

16:39:13

16:39:31 A. **Okay.**

16:39:31 Q. **And do you recognize this document?**

16:39:35 A. **Yes.**

16:39:36 Q. **What is it?**

16:39:37 A. **That is the examiner interview summary record of this**

16:39:44 **interview, which was held in this case.**

16:39:52 Q. **Can you tell when the interview was? Does it**

16:39:56 **indicate?**

16:39:56 A. **No. It's not on this paper, but I -- I recall it.**

16:40:05 Q. **What do you recall? When do you recall the interview**

16:40:08 **took place?**

16:40:09 A. **This was on May 30th, 1995.**

16:40:12 Q. **And if we could go to where the handwriting is in the**

16:40:17 **middle.**

16:40:17 A. **Yes.**

16:40:18 Q. **It's difficult to read. Can you read it?**

16:40:22 A. **Yes. It says, "applicants would present arguments in**

16:40:29 **the present application," and then it says in parentheses,**

16:40:36 **"may file a continuation, to rebut the 101 and 103**

16:40:42 **rejections and may possibly submit declaration for the 112**

16:40:46 **rejection as well as publications. Applicants may also**

16:40:55 **submit some prior art, such as the Chile patent to show they**

16:41:03 **are not prior art over the claims."**

16:41:06 Q. **Who wrote that?**

16:41:08 A. **Examiner Wessendorf.**

16:41:12 Q. **So what was the result of the interview?**

16:41:15 A. **The result was that we want to rebut the 101 and 103 rejections and that we may possibly submit a declaration.**

16:41:34 Q. **And did you file any applications following this interview? In other words, did you file a response, a further response after this interview?**

16:41:45 A. **Yes, we did.**

16:41:46 Q. **What was the next application that you filed?**

16:41:48 A. **We filed a response in this '018 application and after that, we filed another application, a continuation application, the '442 application, which was filed on June 7, 1995.**

16:42:13 Q. **Dr. Wingefeld, are you aware that the defendant in this case has alleged that there was an unreasonable or unexplained delay during the prosecution of the '333 patent during the period of May 31, 1991, to June 6, 1995?**

16:42:45 A. **Yes.**

16:42:46 Q. **Dr. Wingefeld, at any time did you ever take any action to delay anything in this prosecution or the issuance of the '333 patent?**

16:42:57 A. **No.**

16:42:59 Q. **Are you aware of anyone else at Hoechst in the patent department or elsewhere that took any action to try to delay the prosecution of this patent?**

16:43:10 A. **No.**

16:43:11 Q. **Did anyone at the company ever tell you or ask you to take action to delay anything?**

16:43:15 A. **No.**

16:43:16 Q. **Based on your more than 30 years of experience in U.S. patent prosecution, have you ever taken steps to delay a patent application?**

16:43:18 A. **No.**

16:43:27 Q. **Let's talk now about icatibant. Do you know what icatibant is?**

16:43:32 A. **Yes.**

16:43:34 Q. **What is it?**

16:43:34 A. **It's a bradykinin. It has peptides having ten amino acids. Shall I say the sequence?**

16:43:41 Q. **No.**

16:43:41 **THE COURT: No.**

16:43:42 **BY MR. HAUG:**

16:43:52 Q. **You wrote the application on it. Right?**

16:43:59 A. **Yes, I did.**

16:43:59 Q. **Okay. Do you know which group between Groups 1, 2 and 3 that you've testified about, do you know which group icatibant was in?**

16:44:02 A. **Yes. It was in group, it is in Group 1.**

16:44:03 Q. **Do you know which priority filing would relate to icatibant?**

16:44:05 A. **Yes, I know this. This is in Group 1, the second**

16:44:06

16:44:12

16:44:16

16:44:16

16:44:21

16:44:25

16:44:27

16:44:31 filing. The patent, priority patent application filed on
16:44:36 May 19, 1989.
16:44:41 Q. I'd like to turn now to JTX-6.23.
16:44:59 A. Sorry.
16:44:59 Q. Yes.
16:45:00 A. JTX-6?
16:45:07 Q. 230, Page 230.
16:45:25 A. Yes.
16:45:26 Q. Are you with me? Do you know what this document is
16:45:29 that I've directed you to?
16:45:30 A. Yes. This is an amendment, which we filed in the --
16:45:45 which was filed on February 19th, '91.
16:45:50 Q. And did you make any arguments in this response to the
16:45:54 first office action in the '162 file?
16:45:58 A. Yes, we did.
16:46:00 Q. And were those arguments in response to the
16:46:04 rejections -- withdrawn.
16:46:07 I'd like you to turn to Page 232 and the last
16:46:11 sentence.
16:46:12 A. Yes. Yes.
16:46:16 Q. And you see where it says, "applicants respectfully
16:46:22 submit that the in vitro data of the instant specification
16:46:26 is in accord with accepted methods of establishing utility
16:46:29 by in vitro testing of Bradykinin antagonist action using
16:46:34 the modeling disclosed in the specification?"

16:46:36 **Do you see that?**

16:46:37 A. **No. I'm sorry.**

16:46:46 Q. **Okay. Are you on Page 233?**

16:46:52 A. **No. I was on 232. Sorry.**

16:46:56 Q. **Probably because I misspoke. Did I say 232? I apologize.**

16:47:00 A. **I'm sorry.**

16:47:01 Q. **233?**

16:47:02 A. **Yes.**

16:47:02 Q. **And it's the section right below --**

16:47:04 A. **Yes, I see it.**

16:47:05 Q. **Where it's indented.**

16:47:06 A. **Yes.**

16:47:07 Q. **Are you with me now?**

16:47:09 A. **Yes.**

16:47:13 Q. **Do you recall what you were saying here in this application response?**

16:47:19 A. **Yes. We were saying the in vitro data, which are already in this specification, they will establish the utility of those, of the compounds and concept in this patent application.**

16:47:43 Q. **What is the in vitro data?**

16:47:47 A. **In vitro data are data which show efficacy of a compound which, which were not -- those data which didn't come from testing in a living animal. In a living thing,**

16:48:05

16:48:12 **not animal.**

16:48:13 Q. **Was it common practice to include in vitro data in a patent specification?**

16:48:17 A. **Yes.**

16:48:20 Q. **During this time, the prosecution of the '333 patent, was it common practice to include in vivo data?**

16:48:21 A. **No.**

16:48:23 Q. **Why not?**

16:48:26 A. **Those -- we thought according to the rules, to have those in vitro data in, and in vivo data are not necessary to establish this utility.**

16:48:26 Q. **Based on your experience in prosecuting the many cases during the time period of 1991 to 1995, how often did you get a utility, lack of utility, a 101 rejection from the U.S. PTO?**

16:48:27 A. **In those times, that was quite often. So I think that might be approximately in 80 percent of the cases I was involved in prosecution.**

16:48:40 Q. **Did the practice from the U.S. PTO, based on your experience, ever change with respect to rejecting claims for lack of utility under 101?**

16:48:46 A. **Yes.**

16:49:03 Q. **And how did it change?**

16:49:13 A. **Now the U.S. examiners, they don't require in vivo data for showing utility. So in vitro data are sufficient**

16:49:19

16:49:26

16:49:26

16:49:36

16:49:41

16:49:42

16:49:46

16:49:51

16:49:53

16:49:53

16:49:58

16:50:04

16:50:09 to show this utility requirement.

16:50:14 Q. Please turn to JTX-6.323. What is this document?

16:50:27 A. This is a preliminary amendment we filed on August 14th, 1991, in the '149 patent application. In this preliminary amendment, we added new examples, those were Examples 165 through 195. We also submitted additional data, IC50 data for those compounds and also for other compounds, which were already disclosed in the specification.

16:51:18 And we did, also, add new claims, 14 through 17, to this application.

16:51:29 Q. Now, you mentioned that you were now adding 165 to 195 examples. Is that right?

16:51:37 A. Yes.

16:51:38 Q. What were those 195 examples directed to?

16:51:43 A. They were all directed to the claims where we applied for.

16:51:52 Q. Were these examples directed to individual compounds or species?

16:51:57 A. Yes. Those examples were directed to specific compounds, yes.

16:52:02 Q. And was icatibant one of those examples, do you recall?

16:52:07 A. No, it was not one of those additional examples. Icatibant was already disclosed in the specification.

16:52:15 Q. **It was one of the original examples with the**
16:52:18 **application?**
16:52:18 A. **Yes.**
16:52:19 Q. **But it was one of the 195 examples now in the case.**
16:52:23 **Right?**
16:52:23 A. **Yes.**
16:52:23 Q. **Was in vivo data submitted in connection with any of**
16:52:30 **those 195 examples?**
16:52:32 A. **No.**
16:52:32 Q. **Based on your experience, how difficult -- was it**
16:52:43 **difficult to get in vivo data?**
16:52:45 A. **Yes.**
16:52:45 Q. **Why?**
16:52:49 A. **It just was not allowed to do animal testing for each**
16:52:58 **and every compound, was one. So it was allowed to do animal**
16:53:07 **testing only for those compounds where there was a need to,**
16:53:12 **for instance, development compounds, or for those compounds**
16:53:18 **which we most likely were -- will be elected as a**
16:53:28 **development compound.**
16:53:30 Q. **Looking at again Page 323 in the upper left corner, it**
16:53:35 **says "Rule 62 CIP." Do you see that?**
16:53:38 A. **Yes.**
16:53:39 Q. **Do you know what that means, Rule 62 CIP?**
16:53:42 A. **Yes. Rule 62 is a specific number of an application.**
16:53:58 **And Rule 62 is, usually Hoechst did file mainly Rule 62**

16:54:07 **applications because we thought this will result in an**
16:54:12 **earlier response from the Patent Office, and also, the prior**
16:54:18 **patent application was then automatically abandoned.**
16:54:25 Q. **Why did you file additional data and examples in this**
16:54:29 **application after receiving the May 31, 1991 final office**
16:54:37 **action?**
16:54:39 A. **We did this in response to this open final office**
16:54:47 **action, because we at that time thought we had already**
16:54:56 **brought to the examiner our arguments on this. So we wanted**
16:55:03 **to show the examiner that we could underline our patent**
16:55:13 **application with new data and new examples.**
16:55:17 Q. **Please turn to JTX-6. Page 468.**
16:55:30 **Do you recognize this document?**
16:55:33 A. **Yes.**
16:55:34 Q. **What is it?**
16:55:37 A. **This is an office action in the '149 case, which was**
16:55:45 **mailed on July 1st, '92.**
16:55:49 Q. **And does this office action reject Claim 13?**
16:55:57 A. **Yes.**
16:55:58 Q. **Do you know what Claim 13 was directed to at this**
16:56:00 **time?**
16:56:00 A. **At this time, Claim 13 was directed to icatibant.**
16:56:05 Q. **And was Claim 13 rejected on more than one ground in**
16:56:08 **this office action?**
16:56:10 A. **Yes, it was, on various grounds.**

16:56:13 Q. **Please turn to JTX-6.476.**

16:56:20 A. **Yes.**

16:56:20 Q. **And if we go right below the indent, it says Claims 5 to 17 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.**

16:56:38 **Do you see that?**

16:56:38 A. **Yes, I see it.**

16:56:39 Q. **What is your understanding of that rejection?**

16:56:42 A. **The examiner -- those claims were not -- cannot be allowed because somebody else did invent this claimed subject matter. And the examiner goes on and cites two references, which were published in the British Journal of Pharmacology. And those were the articles Hock, et al., and Wirth, et al.**

16:57:22 Q. **Are you saying that the examiner rejected Claim 13 for icatibant under 102(f) based on the argument that they did not invent the subject matter and she was relying on the Wirth article? Is that right?**

16:57:38 A. **Yes.**

16:57:38 Q. **If we go on in the prosecution, why did you file the '052 continuation application, which I believe is the next one. Right?**

16:58:02 A. **Yes. That's the next one.**

16:58:04 **So at that time, from the file history, you can see we had various rejections in also the other groups of**

16:58:25 **patent applications on obviousness-type double patenting.**

16:58:32 **So we were just considering what to do, because**

16:58:36 **we couldn't overcome those rejections in each of those**

16:58:43 **different Groups 1, 2 and 3 on their own. So we were, yes,**

16:58:51 **trying to change strategy and maybe combining those three**

16:58:56 **patent applications.**

16:59:00 **At that time --**

16:59:01 **MR. WIESEN: Your Honor, just to be clear, we**

16:59:04 **are talking about the '052 application?**

16:59:09 **MR. HAUG: That was my question. And she was**

16:59:11 **talking about that and also related to Groups 2 and 3.**

16:59:15 **MR. WIESEN: For the '052 application we have an**

16:59:18 **issue related to the question we raised at sidebar.**

16:59:21 **THE COURT: Well, I think we will take it up**

16:59:23 **tomorrow. If you have a question, we will talk about it.**

16:59:31 **MR. HAUG: I will speak to Mr. Wiesen when we**

16:59:35 **finish.**

16:59:36 **THE COURT: Did you want to ask a final question**

16:59:37 **for the day?**

16:59:39 **MR. HAUG: I think we can break now.**

16:59:42 **THE COURT: Thank you, Doctor. Be careful**

16:59:44 **stepping down. I need to talk to the lawyers for a moment.**

16:59:49 **(Witness steps down from the stand.)**

16:59:51 **THE COURT: So where are we?**

16:59:52 **MR. HAUG: Dr. Wingefeld, obviously, we will**

16:59:57 finish Dr. Wingefeld tomorrow morning. We have --

17:00:00 THE COURT: We may not do it tomorrow morning.

17:00:03 We may not. That's why I want to ask.

17:00:06 MR. HAUG: We only have to finish Dr. Wingefeld,

17:00:09 and then we have short testimony from our last witness, Dr.

17:00:14 Ellis. Then we are finished. We rest.

17:00:16 THE COURT: Mr. Wiesen?

17:00:18 MR. WIESEN: Your Honor, we have a very short

17:00:21 deposition to play from a Shire marketing witness. I think

17:00:25 it's less than ten minutes. Then witnesses responding on

17:00:29 commercial success. So potentially a doctor and an

17:00:32 economist.

17:00:33 THE COURT: How much time?

17:00:34 MR. WIESEN: Short. Two hours maybe total?

17:00:39 That may even include the crosses, two and a half maybe,

17:00:43 with the crosses.

17:00:44 THE COURT: If we begin at 10:30 on Friday, can

17:00:47 we get this done?

17:00:49 MR. HAUG: I don't think there is any problem

17:00:50 with respect to that.

17:00:52 MR. WIESEN: If Mr. Haug says so, then I believe

17:00:55 so, yes.

17:00:57 THE COURT: If I don't have any difficulty

17:00:59 getting back from the airport, then, and we can resume

17:01:03 earlier, just be available.

17:01:05 **Let's plan on 10:30. I would say be here by**
17:01:09 **10:00, yes. All right.**
17:01:11 **Good evening.**
17:01:13 **(Court recessed.)**